Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series

C.-K. Peng
Cardiovascular Division, Harvard Medical School, Beth Israel Hospital, Boston, Massachusetts 02215 and Center for Polymer Studies and Department of Physics, Boston University, Boston, Massachusetts 02215

Shlomo Havlin
Department of Physics, Bar Ilan University, Ramat Gan, Israel

H. Eugene Stanley
Center for Polymer Studies and Department of Physics, Boston, Massachusetts 02215

Ary L. Goldberger
Cardiovascular Division, Harvard Medical School, Beth Israel Hospital, Boston, Massachusetts 02215

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The healthy heartbeat is traditionally thought to be regulated according to the classical principle of homeostasis whereby physiologic systems operate to reduce variability and achieve an equilibrium-like state [Physiol. Rev. **9**, 399–431 (1929)]. However, recent studies [Phys. Rev. Lett. **70**, 1343–1346 (1993); *Fractals in Biology and Medicine* (Birkhauser-Verlag, Basel, 1994), pp. 55–65] reveal that under normal conditions, beat-to-beat fluctuations in heart rate display the kind of long-range correlations typically exhibited by dynamical systems far from equilibrium [Phys. Rev. Lett. **59**, 381–384 (1987)]. In contrast, heart rate time series from patients with severe congestive heart failure show a breakdown of this long-range correlation behavior. We describe a new method—detrended fluctuation analysis (DFA)—for quantifying this correlation property in non-stationary physiological time series. Application of this technique shows evidence for a crossover phenomenon associated with a change in short and long-range scaling exponents. This method may be of use in distinguishing healthy from pathologic data sets based on differences in these scaling properties. © *1995 American Institute of Physics.*

I. INTRODUCTION

Clinicians often describe the normal activity of the heart as "regular sinus rhythm." But in fact cardiac interbeat intervals normally fluctuate in a complex, apparently erratic manner[1,2] [Fig. 1(a)]. This highly irregular behavior has recently motivated researchers[3,4] to apply time series analyses that derive from statistical physics, especially methods for the study of critical phenomena where fluctuations at all length (time) scales occur. These studies show that under healthy conditions, interbeat interval time series exhibit long-range power-law correlations reminiscent of physical systems near a critical point.[5,6] Furthermore, certain disease states may be accompanied by alterations in this scale-invariant (fractal) correlation property. Here we explore the potential utility of such scaling alterations in the detection of pathological states.

Our analysis in this paper is based on the digitized electrocardiograms of beat-to-beat heart rate fluctuations recorded with an ambulatory (Holter) monitor. The time series obtained by plotting the sequential intervals between beat i and beat $i+1$, denoted by $B(i)$, typically reveals a complex type of variability [Fig. 1(a)]. The mechanism underlying such fluctuations appears to be related primarily to countervailing neuroautonomic inputs. Parasympathetic 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 the two branches of the autonomic nervous system is the postulated mechanism for the type of erratic heart rate variability recorded in healthy subjects.[1,7]

An immediate problem facing researchers applying time series analysis to interbeat interval data is that the heartbeat time series is often highly non-stationary. One question is whether this heterogeneous structure arises trivially from changes in environmental conditions having little to do with the intrinsic dynamics of the system itself. Alternatively, these fluctuations may arise from a complex nonlinear dynamical system rather than being an epiphenomenon of environmental stimuli.

From a practical point of view, if the fluctuations driven by uncorrelated stimuli can be decomposed from intrinsic fluctuations generated by the dynamical system, then these two classes of fluctuations may be shown to have very different correlation properties. If that is the case, then a plausible consideration is that only the fluctuations arising from the dynamics of the complex, multiple-component system should show long-range correlations. Other responses should give rise to a different type of fluctuation (although highly non-stationary) having characteristic time scales (i.e. frequencies related to the stimuli). This type of "noise," although physiologically important, can be treated as a "trend" and distinguished from the more subtle fluctuations that may reveal intrinsic correlation properties of the dynamics. To this end, we introduced a modified root mean square analysis of a random walk—termed *detrended fluctuation analysis* (DFA)[8,9]—to the analysis of physiological data. The advan-

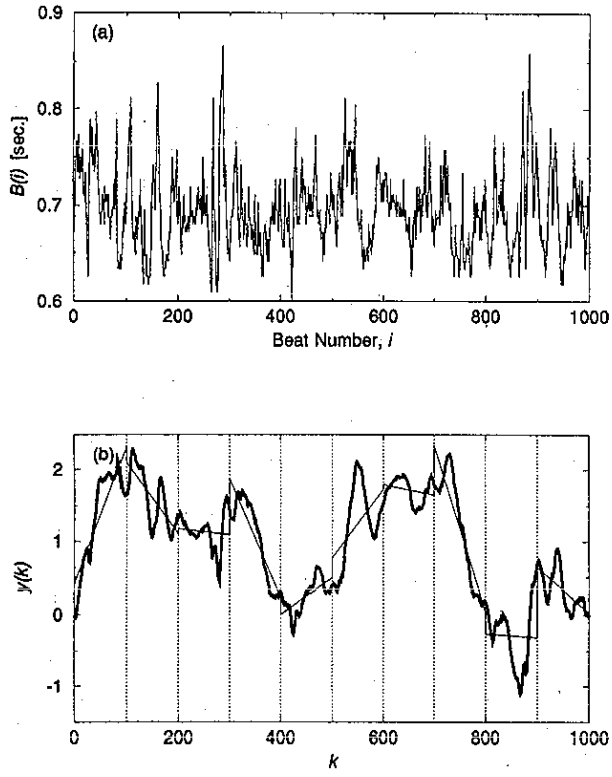

FIG. 1. (a) The interbeat interval time series $B(i)$ of 1000 beats. (b) The integrated time series: $y(k)=\Sigma_{i=1}^{k}[B(i)-B_{\text{ave}}]$, where $B(i)$ is the interbeat interval shown in (a). The vertical dotted lines indicate box of size $n=100$, the solid straight line segments represent the "trend" estimated in each box by a least-squares fit.

tages of DFA over conventional methods (e.g. spectral analysis and Hurst analysis) are that it permits the detection of long-range correlations embedded in a seemingly non-stationary time series, and also avoids the spurious detection of apparent long-range correlations that are an artifact of non-stationarity. This method has been validated on control time series that consist of long-range correlations with the superposition of a non-stationary external trend.[8] The DFA method has also been successfully applied to detect long-range correlations in highly heterogeneous DNA sequences,[8,10,11] and other complex physiological signals.[12]

II. DETRENDED FLUCTUATION ANALYSIS COMPUTATION

To illustrate the DFA algorithm, we use the interbeat time series shown in Fig. 1(a) as an example. Briefly, the interbeat interval time series (of total length N) is first integrated, $y(k)=\Sigma_{i=1}^{k}[B(i)-B_{\text{ave}}]$, where $B(i)$ is the ith interbeat interval and B_{ave} is the average interbeat interval. Next the integrated time series is divided into boxes of equal length, n. In each box of length n, a least-squares line is fit to the data (representing the *trend* in that box) [Fig. 1(b)]. The y coordinate of the straight line segments is denoted by $y_n(k)$. Next we detrend the integrated time series, $y(k)$, by subtracting the local trend, $y_n(k)$, in each box. The root-mean-square fluctuation of this integrated and detrended time series is calculated by

$$F(n)=\sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k)-y_n(k)]^2}. \tag{1}$$

This computation is repeated over all time scales (box sizes) to provide a relationship between $F(n)$, the average fluctuation as a function of box size, and the box size n (i.e. the number of beats in a box which is the size of the window of observation). Typically, $F(n)$ will increase with box size n. A linear relationship on a double log graph indicates the presence of scaling. Under such conditions, the fluctuations can be characterized by a scaling exponent α, the slope of the line relating log $F(n)$ to log n. Consider first a process where the value at one interbeat interval is completely uncorrelated from any previous values, e.g. white noise. This can be achieved by using a time series for which the order of the points has been shuffled (so-called "surrogate" data set). For this type of uncorrelated data, the integrated value, $y(k)$, corresponds to a random walk, and therefore $\alpha=0.5$.[13] If there are only short-term correlations, the initial slope may be different from 0.5, but α will approach 0.5 for large window sizes. An α greater than 0.5 and less than or equal to 1.0 indicates persistent long-range power-law correlations such that a large (compared to the average) interbeat interval is more likely to be followed by large interval and vice versa. In contrast, $0<\alpha<0.5$ indicates a different type of power-law correlation such that large and small values of the time series are more likely to alternate.[14] A special case of $\alpha=1$ corresponds to $1/f$ noise.[5,15] For $\alpha\geq 1$, correlations exist but cease to be of a power-law form; $\alpha=1.5$ indicates *Brown* noise, the integration of white noise. The α exponent can also be viewed as an indicator that describes the "roughness" of the original time series: the larger the value of α, the smoother the time series. In this context, $1/f$ noise can be interpreted as a "compromise" between the complete unpredictability of white noise (very rough "landscape") and the very smooth "landscape" of Brownian noise.[16,17]

Figure 2 compares the DFA analysis of representative 24 hour interbeat interval time series of a healthy subject (○) and a patient with congestive heart failure (△). Notice that for large time scales (asymptotic behavior), the healthy subject interbeat interval time series shows almost perfect power-law scaling over two decades ($20\leq n\leq 10000$) with $\alpha=1$ (i.e., $1/f$ noise) while for the pathologic data set $\alpha\approx 1.3$ (closer to Brownian noise). This result is consistent with our previous finding that there is a significant difference in the long-range scaling behavior between healthy and diseased states.[3,4]

III. NORMAL VS PATHOLOGIC TIME SERIES

To test for statistical significance using the DFA method, we re-analyzed cardiac interbeat data from two different groups of subjects reported in our previous work:[3] 12 healthy adults without clinical evidence of heart disease (age range: 29–64 years, mean 44) and 15 adults with severe heart failure (age range: 22–71 years; mean 56).[18] Data from each subject comprise approximately 24 hours of ECG recording. Data from patients with heart failure due to severe left ven-

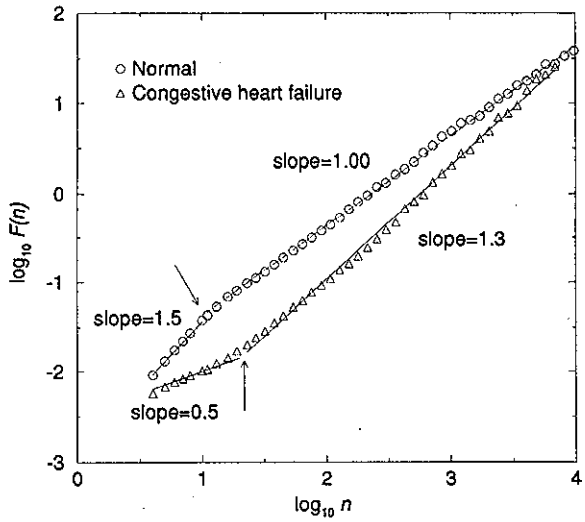

FIG. 2. Plot of log $F(n)$ vs log n (see description of DFA computation in text) for two very long interbeat interval time series (~24 hours). The circles are from a healthy subject while the triangles are from a subject with congestive heart failure. Arrows indicate "crossover" points in scaling.

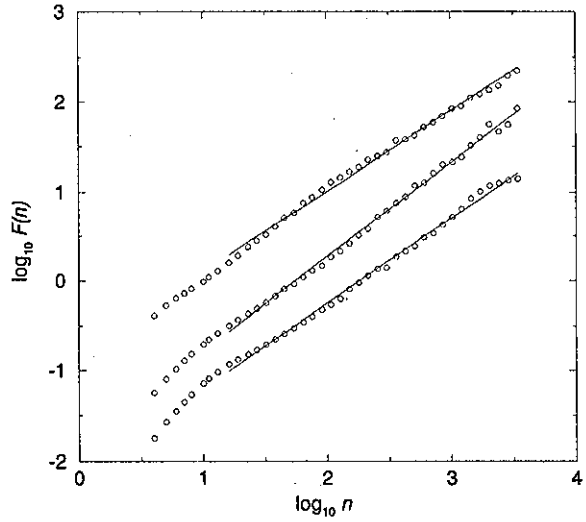

FIG. 3. Plot of log $F(n)$ vs log n of 3 data subsets (each contains approximately 8 hours of data) from the same subject. The resulting plots were shifted vertically for purpose of display. The α exponents obtained over the same fitting range (from 16 to 3400 beats) are very similar: 0.90, 1.05 and 0.95, respectively. Note that not all three data sets exhibit crossover in scaling behavior.

tricular 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[19] 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 (~1 cycle/minute) heart rate oscillations associated with the well-recognized syndrome of periodic (Cheyne–Stokes) respiration, an abnormal breathing pattern often associated with low cardiac output.[19]

We observe the following scaling exponent (for time scale $10^2 \sim 10^4$ beats) for the group of healthy cardiac interbeat interval time series (mean value ±S.D.): $\alpha = 1.00 \pm 0.11$.[20] This result is consistent with previous reports of $1/f$ fluctuations in healthy heart rate (by spectral analysis).[21,22] The pathologic group shows a significant ($p < 0.01$ by Student's t-test) deviation of the long-range correlation exponent from normal. For the group of heart failure subjects, we find that $\alpha = 1.24 \pm 0.22$. Of interest, some of the heart failure subjects show an α exponent very close to 1.5 (Brownian noise), indicating random walk-like fluctuations, also consistent with our previous findings in this group. The group-averaged exponent α is less than 1.5 for the heart failure patients, suggesting that pathologic dynamics may only transiently operate in the random walk regime or may only approach this extreme state as a limiting case. We obtained similar results when we divided the time series into three consecutive subsets (of ~8 hours each) and repeated the above analysis. Therefore our findings are not simply attributable to different levels of daily activities (see Fig. 3).

IV. CROSSOVER PHENOMENA

Although this asymptotic scaling exponent may serve as a useful index for selected diagnostic purposes, a drawback is that very long data sets are required (at least 24 hours) for statistically robust results. For practical purposes, clinical investigators are usually interested in the possibility of using substantially shorter time series. In this regard, we note that for short time scales, there is an apparent *crossover* exhibited for the scaling behavior of both data sets (arrows in Fig. 2). For the healthy subject, the α exponent estimated from very small n (< 10 beats) is larger than that calculated from large n (> 10 beats). This is probably due to the fact that on very short time scales (a few beats to ten beats), the physiologic interbeat interval fluctuation is dominated by the relatively smooth heartbeat oscillation associated with respiration, thus giving rise to a large α value. For longer scales, the interbeat fluctuation, reflecting the intrinsic dynamics of a complex system, approaches that of $1/f$ behavior as previously noted. *In contrast, the pathologic data set shows a very different crossover pattern* (Fig. 2). For very short time scales, the fluctuation is quite random (close to white noise, $\alpha \approx 0.5$). As the time scale becomes larger, the fluctuation becomes smoother (asymptotically approaching Brownian noise, $\alpha \approx 1.5$). These findings are consistent with our previous report of altered correlation properties under pathologic conditions.[3,4] At present it is unclear why we observe such alteration. Nevertheless, a good quantitative description can probably advance our understanding.

V. STOCHASTIC MODEL FOR PATHOLOGIC DATA

The physiologic mechanism for the long-range correlations represented by the $1/f$ spectrum of normal interbeat intervals remains to be established. Both stochastic and de-

terministic models have been proposed to account for such scale-invariant behavior in physical systems. We introduce a simple three-parameter stochastic model (without relating to actual neuroautonomic control mechanisms) that can quantitatively describe the crossover scaling behavior *under extreme pathologic conditions.* The simple stochastic model is based on two assumptions:

(i) For short time scales (less than 10−20 beats) the cardiac interbeat intervals with congestive heart failure can be described as white noise. Consider that the sinus node tends to maintain a constant ("homeostatic") firing rate. However, the actual beat-to-beat time intervals will deviate from a perfectly regular oscillation due to random fluctuations described by a distribution with a zero mean value and a well-defined variance (Δ^2). The typical period (the characteristic time) that the sinus node keeps its firing rate constant is denoted by τ.

(ii) The system responds to other driving forces (environmental influences or intrinsic factors) by increasing or decreasing the firing rate. The typical change of the firing rate is characterized by a parameter δ. Once the sinus node adjusts its firing rate, it will tend to maintain it for a period of τ beats as described in (i).

Figure 4 shows the comparison of the actual interbeat data for one of the heart failure subjects to that generated by the model. The effect of assumption (i) is to generate white noise for time-scale less than τ; i.e., if we let $\tau \to \infty$ then the DFA plot of this model will be a straight line with slope 0.5 for all ranges of n. On the other hand, the effect of (ii) is to create the kind of noise associated with Brownian motion ("brown noise"), i.e., if we set τ very small ($\sim$ 1 beat) then the DFA plot will be a straight line with slope 1.5. In order to simulate the observed *crossover* between these two regimes, we need to set τ in the model to be of the same order as the crossover time observed in Fig. 4(c). Beside the parameter τ, we only need to select the other two parameters, Δ^2 and δ, to fit the observed data.

The simple model described above is useful because it shows how two apparently different pathologic scaling mechanisms are in fact connected by the emergence of a characteristic time, corresponding to the observed "crossover" behavior of the real data. However, this model is limited in its scope because it (i) does not account for the $1/f$ ($\alpha = 1$) scaling behavior of the healthy heart rate dynamics, and (ii) it does not relate the parameters to specific neuroautonomic control mechanisms. We note that this model implies that under extreme pathologic conditions, the system attempts to maintain a constant interbeat interval for short time scales while responding to other factors over longer time scales by a smooth variation of the interbeat interval. This behavior is dramatically different from the observed dynamics of interbeat interval under normal (healthy) condition which shows a more complex pattern of sinus rhythm fluctuations than can be accounted for with traditional homeostasis models.[23]

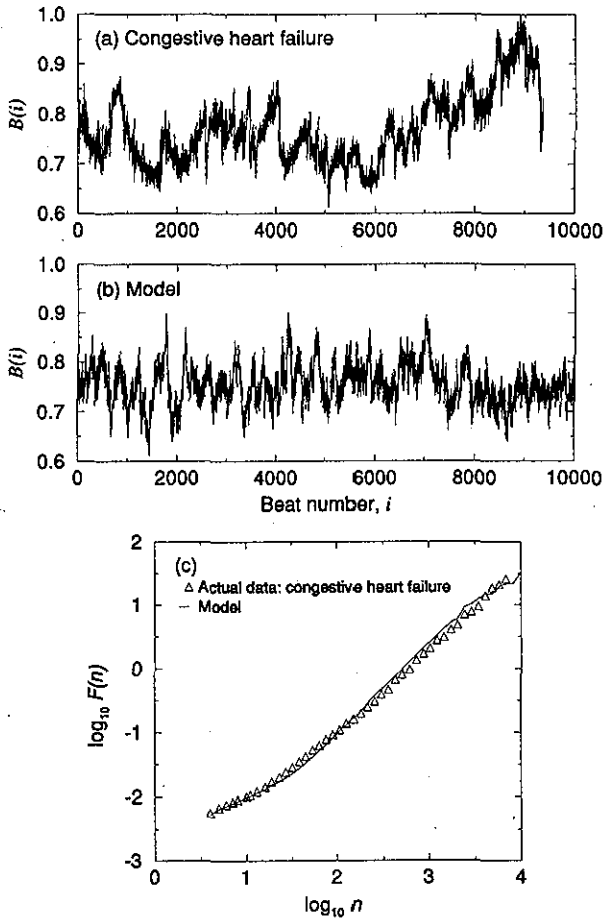

FIG. 4. (a) Interbeat interval time series from a patient with heart failure (the same subject described in Fig. 2). (b) Time series generated by model. Only part of the total time series is shown here. (c) The DFA of the interbeat interval function $B(i)$ for data in (a) and (b). The triangles represent actual data from the subject and the solid lines are generated by the model. The actual simulation of the model is carried out as follows: (i) Choose a firing rate, R_1, such that $B(1)$ equal to the average value, $\bar{B}$, of the real interbeat data set. (ii) The subsequent interbeat values will be $B(1)$ plus a random fluctuation (described by a distribution with zero mean and a finite variance, Δ^2). (iii) With a probability $1/\tau$, the firing rate R_1 will change to a new value $R_2 = R_1 + \xi$. The magnitude of this drift, ξ, is random and described by a distribution with zero mean and standard deviation δ. For this simulation, the value of the parameters are: $\tau = 20$ beats, $\Delta = 0.011$ s and $\delta = 0.008$ s. The parameter τ is chosen to fit the crossover time, where Δ and δ are chosen for fitting the data over short and long time scales, respectively. To account for the physiological constraint that the firing rate cannot become arbitrarily large or small, we also add a instantaneous restoring force that is proportional to the difference between the current firing rate and the mean (average) firing rate (measured from the actual data). This restoring force only affects very long time scales ($\sim 10^4$) fluctuations.

VI. CLINICAL APPLICATION: PRELIMINARY RESULTS

The above observation of a differential crossover pattern for healthy versus pathologic data motivated us to extract two parameters from each data set by fitting the scaling exponent α over two different time scales: one short, the other long. To be more precise, for each data set we calculated an exponent α_1 by making a least squares fit of $\log F(n)$ vs $\log n$ for $4 \leqslant n \leqslant 16$. Similarly, an exponent α_2 was obtained from $16 \leqslant n \leqslant 64$. Since these two exponents are not extracted from the asymptotic region, relatively short data sets are sufficient, thereby making this technique applicable to "real world" clinical data.

We applied this quantitative fluctuation analysis to the two different groups of subjects mentioned above to measure

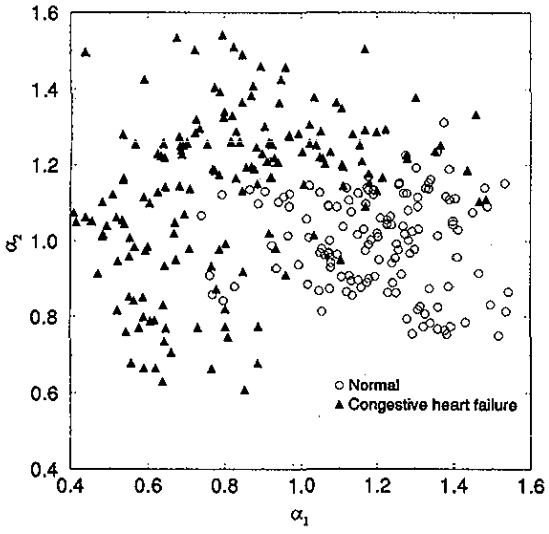

FIG. 5. Scatter plot of scaling exponents α_1 vs α_2 for the healthy subjects (○) and subjects with congestive heart failure (△). The α's were calculated from interbeat interval data sets of length 8192 beats. Longer data set records were divided into multiple data sets (each with 8192 beats). Note good separation between healthy and heart disease subjects, with clustering of points in two distinct "clouds."

the two scaling exponents α_1 and α_2. The two exponents were calculated for each data set of length $N=8192$ beats ($\sim$ 2 hours) and longer data set records were divided into multiple subsets (each with 8192 beats). For healthy subjects, we find the following exponents (mean value $\pm$ S.D.) for the cardiac interbeat interval time series: $\alpha_1=1.201\pm0.178$ and $\alpha_2=0.998\pm0.124$. For the group of congestive heart failure subjects, we find that $\alpha_1=0.803\pm0.259$ and $\alpha_2=1.125\pm0.216$, both significantly ($p<0.0001$ for both α_1 and α_2) different from normal. Furthermore, we show in Fig. 5 that fairly good discrimination between these two groups can be achieved by using these two scaling exponents. We note that not all subjects in our preliminary study show an obvious crossover in their scaling behavior. Only 8 out of 12 healthy subjects exhibited this crossover, while 11 out of 15 pathologic subjects exhibited a "reverse" crossover. However, the two scaling exponents (α_1 and α_2) measured from relatively short data sets can still be potentially useful indicators to distinguish normal from pathologic time series.[24]

To test the effect of data length on these calculations, we repeated the same DFA measurements for longer data sets ($N=16384$) and also for shorter data sets ($N=4096$). As expected, the results for shorter data sets are less reliable (more overlap between two groups) due to anticipated statistical error related to finite sample size.[25] On the other hand, longer data sets result in little improvement for the distinction between groups. Therefore, the data length of 8192 seems to be a statistically reasonable choice.[26]

Furthermore, we note that data from normal interbeat interval time series are tightly clustered suggesting that there may exist a "universal" scaling behavior for physiologic interbeat time series. In contrast, the pathologic data show more variation, a finding which may be related to different clinical conditions and varying severity of the pathologic states.

VII. CONCLUSION

In summary, we apply a new fluctuation analysis (modified from classical random walk analysis) to the nonstationary heartbeat time series from healthy subjects and those with severe heart disease (congestive heart failure). We show that this method is capable of identifying crossover behavior due to differences in scaling over short versus long time scales. This finding is of interest from a physiologic viewpoint since it motivates new modeling approaches to account for the control mechanisms regulating cardiac dynamics on different time scales. From a practical point of view, quantification of these scaling exponents may have potential applications for bedside and ambulatory monitoring.

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[1] R. I. Kitney and O. Rompelman, *The Study of Heart-Rate Variability* (Oxford University Press, Oxford, 1980).
[2] A. L. Goldberger, D. R. Rigney, and B. J. West, Sci. Am. **262**, 42–49 (1990).
[3] C.-K. Peng, J. Mietus, J. M. Hausdorff, S. Havlin, H. E. Stanley, and A. L. Goldberger, Phys. Rev. Lett. **70**, 1343–1346 (1993).
[4] C.-K. Peng, S. V. Buldyrev, J. M. Hausdorff, S. Havlin, J. E. Mietus, M. Simons, H. E. Stanley, and A. L. Goldberger, in *Fractals in Biology and Medicine*, edited by T. F. Nonnenmacher, G. A. Losa, and E. R. Weibel (Birkhaüser-Verlag, Basel, 1994), pp. 55–65.
[5] P. Bak, C. Tang, and K. Wiesenfeld, Phys. Rev. Lett. **59**, 381–384 (1987).
[6] H. E. Stanley, *Introduction to Phase Transitions and Critical Phenomena* (Oxford University Press, London, 1971).
[7] M. N. Levy, Circ. Res. **29**, 437–445 (1971).
[8] C.-K. Peng, S. V. Buldyrev, S. Havlin, M. Simons, H. E. Stanley, and A. L. Goldberger, Phys. Rev. E **49**, 1691–1695 (1994).
[9] Computer software of DFA algorithm is available upon request; contact C.-K. Peng (e-mail: peng@chaos.bih.harvard.edu).
[10] S. V. Buldyrev, A. L. Goldberger, S. Havlin, C.-K. Peng, H. E. Stanley, and M. Simons, Biophys. J. **65**, 2675–2681 (1993).
[11] S. M. Ossadnik, S. V. Buldyrev, A. L. Goldberger, S. Havlin, R. N. Mantegna, C.-K. Peng, M. Simons, and H. E. Stanley, Biophys. J. **67**, 64–70 (1994).
[12] J. M. Hausdorff, C.-K. Peng, Z. Ladin, J. Y. Wei, and A. L. Goldberger, J. Appl. Physiol. **78**, 349–358 (1995).
[13] E. W. Montroll and M. F. Shlesinger, in *Nonequilibrium Phenomena II. From Stochastics to Hydrodynamics*, edited by J. L. Lebowitz and E. W. Montroll (North-Holland, Amsterdam, 1984), pp 1–121.
[14] S. Havlin, R. B. Selinger, M. Schwartz, H. E. Stanley, and A. Bunde, Phys. Rev. Lett. **61**, 1438–1441 (1988).
[15] W. H. Press, Comments Astrophys. **7**, 103–119 (1978).
[16] C.-K. Peng, S. Buldyrev, A. L. Goldberger, S. Havlin, F. Sciortino, M. Simons, and H. E. Stanley, Nature **356**, 168–170 (1992).
[17] S. V. Buldyrev, A. L. Goldberger, S. Havlin, C.-K. Peng, and H. E. Stanley, in *Fractals in Science*, edited by A. Bunde and S. Havlin (Springer-Verlag, Berlin, 1994), pp. 48–87.
[18] ECG recordings of Holter monitor tapes were processed both manually and in a fully automated manner using our computerized beat recognition

algorithm (Aristotle). Abnormal beats were deleted from each data set. The deletion has practically no effect on the DFA analysis since less than 1% of total beats were removed. Patients in the heart failure group were receiving conventional medical therapy prior to receiving an investigational cardiotonic drug; see D. S. Baim *et al.*, J. Am. Coll. Cardiol. **7**, 661–670 (1986).

[19] A. L. Goldberger, D. R. Rigney, J. Mietus, E. M. Antman, and S. Greenwald, Experientia **44**, 983–987 (1988).

[20] Typical regression fit shows excellent linearity of double log graph (indicated by correlation coefficient $r>0.97$) for both groups. However, usually data from healthy subjects show even better linearity on log–log plots than data from subjects with heart disease. Our estimate of α is consistent with the previous analysis in Ref. 3. Note, however, that in Ref. 3 the analysis was performed on the interbeat *increment* data to avoid the problem of non-stationarity. Therefore, the scaling exponent computed in Ref. 3 is smaller than the α exponent computed by DFA by a value of 1 (due to the integration process in DFA).

[21] A. L. Goldberger and B. J. West, Yale J. Biol. Med. **60**, 421–435 (1987).

[22] M. Kobayashi and T. Musha, IEEE Trans. Biomed. Eng. **BE-29**, 456–457 (1982).

[23] W. B. Cannon, Physiol. Rev. **9**, 399–431 (1929).

[24] A further refinement (not presented here) may be obtained by not arbitrarily setting the crossover scale to be 16 beats for all data sets. Instead, each individual data set could have its own ranges for fitting α_1 and α_2 that depend on the specific crossover point in the given data set.

[25] C.-K. Peng, S. V. Buldyrev, A. L. Goldberger, S. Havlin, M. Simons, and H. E. Stanley, Phys. Rev. E **47**, 3730–3733 (1993).

[26] We also tested these calculations by varying the fitting range for α_2. We find that the results are very similar when we measure α_2 from 16 beats to 128 beats. However, when we move the upper fitting range for α_2 from 128 beats to 256 beats or more, the pathologic data sets show larger variation of α_2 leading to less obvious separation from normal subjects. This is partly due to the fact that, for finite length data sets, the calculation error of $F(n)$ increases with n.[25] Therefore, scaling exponents obtained over larger values of n will have greater uncertainty.