Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics

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Nikhil Iyengar, C.-K. Peng, Raymond Morin, Ary L. Goldberger, and Lewis A. Lipsitz. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *Am. J. Physiol.* 271 (*Regulatory Integrative Comp. Physiol.* 40): R1078–R1084, 1996.—We postulated that aging is associated with disruption in the fractallike long-range correlations that characterize healthy sinus rhythm cardiac interval dynamics. Ten young (21–34 yr) and 10 elderly (68–81 yr) rigorously screened healthy subjects underwent 120 min of continuous supine resting electrocardiographic recording. We analyzed the interbeat interval time series using standard time and frequency domain statistics and using a fractal measure, detrended fluctuation analysis, to quantify long-range correlation properties. In healthy young subjects, interbeat intervals demonstrated fractal scaling, with scaling exponents (α) from the fluctuation analysis close to a value of 1.0. In the group of healthy elderly subjects, the interbeat interval time series had two scaling regions. Over the short range, interbeat interval fluctuations resembled a random walk process (Brownian noise, $\alpha = 1.5$), whereas over the longer range they resembled white noise ($\alpha = 0.5$). Short (α_s)- and long-range (α_l) scaling exponents were significantly different in the elderly subjects compared with young ($\alpha_s = 1.12 \pm 0.19$ vs. 0.90 ± 0.14, respectively, $P = 0.009$; $\alpha_l = 0.75 \pm 0.17$ vs. 0.99 ± 0.10, respectively, $P = 0.002$). The crossover behavior from one scaling region to another could be modeled as a first-order autoregressive process, which closely fit the data from four elderly subjects. This implies that a single characteristic time scale may be dominating heartbeat control in these subjects. The age-related loss of fractal organization in heartbeat dynamics may reflect the degradation of integrated physiological regulatory systems and may impair an individual's ability to adapt to stress.

heart rate; cardiovascular control; modeling

SEVERAL RECENT STUDIES (3, 8, 18, 20, 22, 23) have shown that the normal beat-to-beat fluctuations of the healthy sinus rhythm heartbeat are neither strictly regular nor completely random, but demonstrate an underlying fractallike structure, characterized by the presence of similar dynamic behaviors operating over multiple scales in time (long-range correlations). It is likely that the complex dynamics of the healthy heartbeat arise from numerous coupled control systems and feedback loops that regulate the cardiac cycle on different time scales (10).

Aging has a profound impact on many of the interacting neural and endocrine mechanisms that regulate heart rate (10, 12). Parasympathetic and sympathetic influences become attenuated, renin and angiotensin levels fall, and circadian hormonal and temperature rhythms lose amplitude (11). The heart rate time series loses much of its complex, irregular behavior (10, 12). This change in cardiac dynamics has been quantified by statistics such as "approximate entropy" and "approximate dimension," which are lower in healthy elderly subjects compared with young (7, 19). Furthermore, power spectral analysis reveals a relative loss of higher frequency heart rate fluctuations, suggesting a change in the fractal scaling that characterizes healthy heart rate dynamics (13).

However, several methodological issues limit the interpretation of previous studies. First, previously applied statistical measures are highly sensitive to nonstationarities in time series data and therefore cannot identify the underlying structure of physiological fluctuations if there are trends due to external environmental influences. As a result, some previous studies have examined relatively short stationary data sets that are not long enough to determine correlation properties over multiple time scales (7, 13, 19). One study examined longer time series, but these were derived from ambulatory cardiac recordings that are highly influenced by activity, sleep, and other factors that may produce problematic trends in the data (4). Finally, previous studies of aging are limited by the lack of rigorous screening procedures to exclude the presence of occult coronary artery disease in elderly subjects.

We recently introduced the technique of detrended fluctuation analysis (DFA), based on a modified root mean square analysis of a random walk, to assess the intrinsic correlation properties of a dynamic system separated from external trends in the data (16). The present study applied this technique to 2 h of continuous electrocardiographic data gathered from rigorously screened, healthy young and old subjects during wakeful supine rest. Our aim was to test the hypothesis that aging, in the absence of disease or nonstationary environmental influences, is associated with an alteration in long-range (fractal) correlations in sinus rhythm interbeat interval dynamics.

METHODS

Subjects. Two groups of healthy human subjects, 10 young (mean age 27 yr, range 21–34 yr) and 10 elderly (mean age 74 yr, range 68–81 yr), participated in this study. Each group consisted of five women and five men. All subjects provided written informed consent and underwent a screening history, physical examination, routine blood count and biochemical

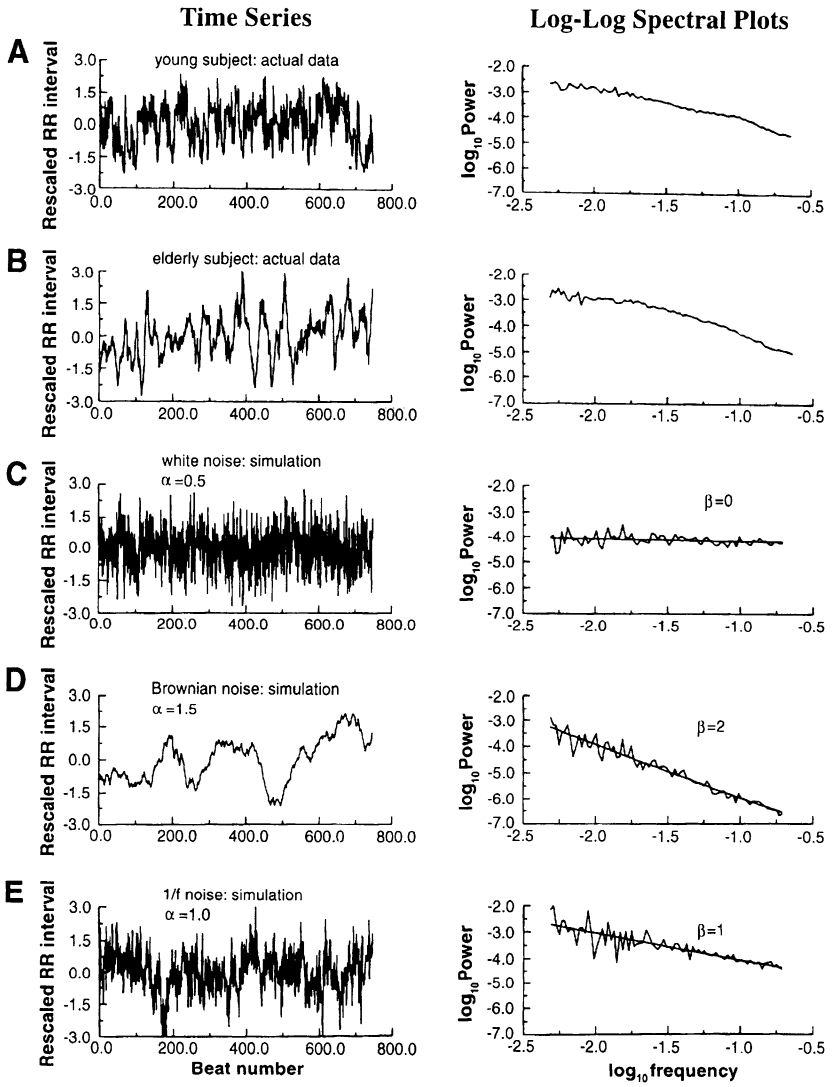

Fig. 1. Interbeat interval time series (*left*) and their corresponding frequency spectra (*right*, plotted as log power vs. log frequency) for a young and old subject are shown in *A* and *B*, respectively. To account for differences in the mean and variance of interbeat intervals between young and elderly subjects, the amplitude of R-R interval fluctuations is rescaled as SD units centered around a mean of zero. Thus the visible difference in the structures of the time series is related to their dynamic properties (sequential ordering in time) rather than their interbeat interval distributions. Also shown are time series and frequency spectra for three types of dynamic behavior. White noise (*C*) is a sequence of independent random values with $\alpha = 0.5$, representing no correlation between values. Frequency spectrum is horizontal with equal power in all frequencies and a corresponding β-exponent of 0. Brownian noise (*D*), also known as a random walk, has $\alpha = 1.5$ and $\beta = 2$, indicating presence of short-term correlations and, consequently, a large amplitude of fluctuation for values that are relatively far apart (i.e., low frequency). Fractal ($1/f$) noise (*E*) shows long-range correlations, with an α and β of 1.0.

analysis, electrocardiogram (ECG), and exercise tolerance test. Only healthy, nonsmoking subjects with normal exercise tolerance tests, no medical problems, and taking no medications were admitted to the study.

Protocol. Subjects lay supine for 120 min while continuous ECG signals were collected. All subjects remained in an inactive state in sinus rhythm while watching the movie "Fantasia" (Disney) to help maintain wakefulness. The continuous ECG was digitized at 250 Hz. Each heartbeat was annotated using an automated arrhythmia detection algorithm, and each beat annotation was verified by visual inspection. The R-R interval (interbeat interval) time series for each subject was then computed. This time series was used for the DFA. A Fourier power spectrum analysis was also performed on the original R-R interval time series, but without detrending.

Analysis of correlations: DFA. Fluctuations in any interbeat interval time series can be usefully analyzed by comparing their behavior to various types of "noise" seen in dynamic systems (Fig. 1). The noisy signals produced by these systems have different statistical correlations that reveal important properties of their dynamics.

With white noise, no correlations exist in the time series, and the sequence of interbeat intervals is completely random (Fig. 1*C*). The frequency spectrum of white noise is flat, because all frequencies are present in equal intensity (power) across the entire spectrum (like white light, in which each of the component colors has equal intensity). Alternatively, there may be short-range correlations in the time series that decay rapidly as the data points move further apart. This type of short-range correlation is very common in nature. One extreme example is the so-called random walk or Brownian noise (Fig. 1*D*). In this case, the interbeat interval at any given instant is strongly correlated to the previous interval. The frequency spectrum for a random walk process is characterized by a rapidly decaying smooth curve in which the amount (power) of the fluctuation is inversely proportional to the frequency squared ($1/f^2$). The exponent 2 in this "power law" relationship between frequency and power is called the scaling exponent β.

Another type of noise that is commonly encountered in nature exhibits persistent long-range correlations (1, 14); i.e., the value at every point is partially dependent on the values at all previous points. This is called "$1/f$ noise" (Fig. 1*E*). The frequency spectrum is also a smooth curve, but the amplitude of fluctuations is inversely proportional to the first power of frequency ($1/f$, $\beta = 1$), obeying the $1/f$ power law of fractallike processes. $1/f$ Noise is usually associated with the dynamic behavior of time series generated by complex systems that have multiple time scales. By visual inspection, the young and old subjects' interbeat interval time series shown in Fig.

1, *A* and *B*, appear to share features with the different noises in Fig. 1, *C-E*.

One way to quantify the dynamic differences in the interbeat interval time series is to apply standard Fourier analysis techniques and calculate the β-exponent in the power law relating frequency to power (8, 13). This exponent is simply the negative slope of the regression line drawn through the log-log plot of power vs. frequency. A β-exponent (slope) of 0 represents the flat spectrum of white noise, whereas other values suggest that there are correlations in the data. A value close to 1 indicates the presence of a fractal process with long-range correlations, whereas a value close to 2 suggests there are primarily short-term correlations analogous to a random walk (see Fig. 1).

One drawback of the power spectrum analysis is that it is highly influenced by nonstationarities in the data, making the β-exponent estimate unreliable. Therefore, we also used DFA (16) for more accurate measurement of the correlation properties. This method permits the detection of correlations embedded in a seemingly nonstationary time series and avoids the spurious detection of apparent long-range correlations that are an artifact of nonstationarities. Because the detrending procedure is implemented on all scales, DFA can be used to quantify the self-similar properties of a signal. DFA has been previously validated (21) and successfully applied to detect long-range correlations in highly heterogeneous DNA sequences (2, 15) and other complex physiological signals (6).

To illustrate the DFA algorithm, we use the interbeat interval time series shown in Fig. 2*A* as an example. The total length of the interbeat interval time series (N) is first integrated

$$y(k) = \sum_{i=1}^{k} [\text{R-R}(i) - \text{R-R}_{\text{avg}}]$$

where R-R(i) is the ith interbeat interval and R-R$_{\text{avg}}$ is the average interbeat interval. Next, the integrated time series is divided into boxes of equal length n (Fig. 2, *B* and *C*). In each box of length n, a least-squares line is fit to the data (representing the trend in that box) (Fig. 2*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

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

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 (Fig. 2, *B-D*). In this study, box size ranged from 4 to ~300 beats. A box size larger than 300 beats would give a less accurate fluctuation value because of the finite-length effects of the data (15).

Typically, $F(n)$ will increase with box size (Fig. 2*D*). A linear relationship on a double-log graph indicates the presence of scaling, i.e., $F(n) \approx n^{\alpha}$. 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 (Fig. 2*D*). An α of 0.5 corresponds to white noise, α = 1 represents 1/*f* noise, and α = 1.5 indicates Brownian noise or a random walk. The exponent α is related to β by a simple formula (15): α = (1 + β)/2.

Crossover phenomena. A good linear fit of the log $F(n)$ vs. log n plot (DFA plot) indicates that $F(n)$ is proportional to n^{α}, where α is the single exponent describing the correlation

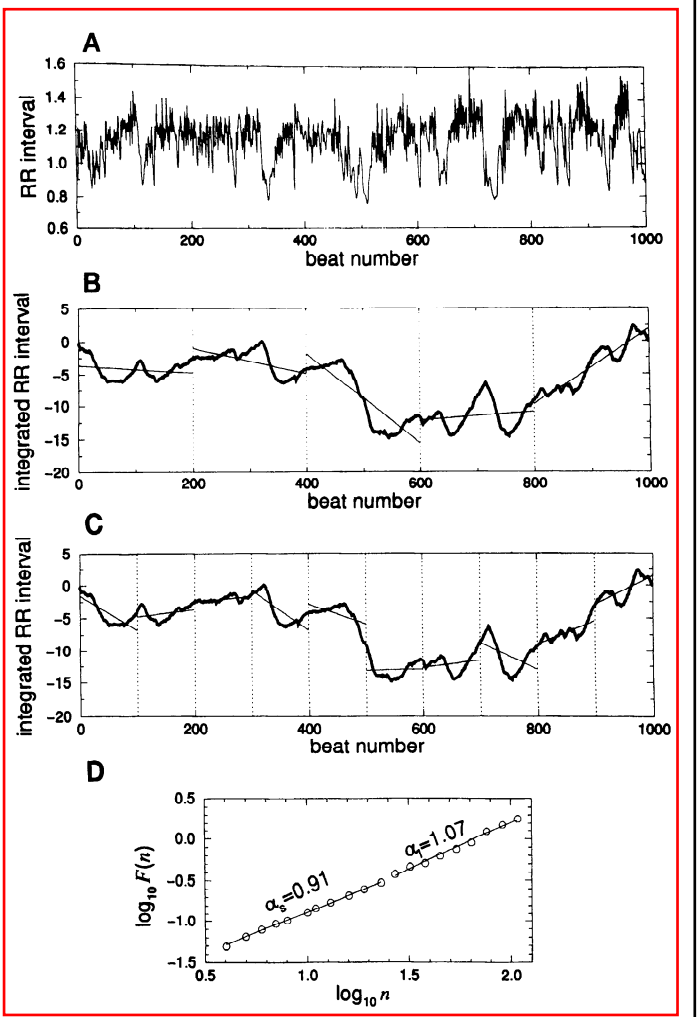

Fig. 2. Detrended fluctuation analysis: interbeat interval time series (*A*) is integrated and shown by the heavy curve in *B*. Vertical dotted lines indicate a box of size n = 200 beats; solid straight line segments represent the "trend" estimated in each box by a linear least-squares fit. At this box size, the fluctuation of the curve around the trend, $F(200)$, is calculated. When the box size is decreased to 100 (*C*), the trends more accurately fit the curve and the fluctuation value decreases. *D*: $F(n)$ plotted against several box sizes, n, on a log-log scale. Curve is approximately linear over 2 regions with a slope α_s for small box sizes and α_l for larger box sizes.

properties of the entire range of time scales. However, in some of the subjects' interbeat interval time series we found that the DFA plot was not strictly linear but rather consisted of two distinct linear regions of different slopes separated at a break point n_{bp}. This observation suggests there is a short-range scaling exponent, α_s, over periods of 4 to n_{bp} beats, and a long-range exponent, α_l, over longer periods.

To systematically identify the break point for each subject, we examined the second derivative of the DFA plot. Because the ideal break point separates two linear regions of different slopes, we placed the break point between the two regions of relatively stable slope, at the point where the slope was changing most rapidly. The second derivative function, $d^2/d(\log_{10}n)^2$ [$\log_{10}F(n)$], has local extrema at such points, and the break points were chosen to coincide with these extrema.

Statistical analysis. Statistical comparisons between groups of young and elderly subjects were conducted using Student's *t*-test. A $P < 0.05$ was considered statistically significant.

RESULTS

The mean heart rates of the young and elderly subjects were similar. Although the standard deviation of heart rate was significantly greater in the young subjects compared with the old ($P < 0.0001$; Table 1), this measure of variance does not provide information about the dynamic properties of the time series. Figure 1 shows the interbeat intervals for representative young and elderly subjects in *A* and *B*, respectively. The difference in the dynamic behavior of the two interbeat interval time series is visually apparent. The scaling exponents of the interbeat interval time series are independent of the mean and SD and provide additional information about the underlying structure of the data.

The results of the power spectral analysis are shown in Table 1. The group of older subjects tended to have a larger β-exponent (more negative slope) than the younger subjects, consistent with previous results (13). However, this difference did not quite reach statistical significance.

Within the entire group of 20 subjects, n_{bp} usually ranged from 25 to 30 heartbeats. Therefore, α_s (short-range exponent) represents correlations on a scale of 30 beats or less, and α_l (long-range exponent) represents correlations on a scale lasting from the length of 40 beats to 10 min. The average values of α_s and α_l for the young and old subjects are shown in Table 1. There was a highly significant difference between α_s and α_l for elderly subjects ($P = 0.0002$), but not for the young ($P = 0.14$).

Figure 3 is a scatter plot showing the distribution of individual α_s and α_l values among the 20 subjects. The plot reveals that most of the older subjects have a larger α_s compared with the young, tending more toward a value of 1.5 (Brownian noise). For α_l, most of the young subjects' values are clustered around 1 (1/*f* noise), whereas for most of the elderly subjects α_l is lower, closer to a value of 0.5 (white noise). The differences in these scaling exponents between young and elderly groups are statistically significant (Table 1).

Model development for crossover phenomena. As indicated above, elderly subjects exhibited crossover behavior in their interbeat interval scaling exponents, from a higher value of α (close to Brownian noise) for fluctuations on small time scales, to a lower value of α (close to white noise) for larger time scales. We modeled this type of crossover behavior by a simple stochastic model from time series analysis, a first-order autoregressive process: $\text{R-R}(i+1) = a\text{R-R}(i) + \epsilon(i)$, where $\epsilon(i)$ is a random variable chosen from a Gaussian distribution. The model simply states that the next interbeat interval, R-R(i + 1), combines two inputs: *1*) stochastic noise (ϵ) of the system and *2*) information about the present interbeat interval R-R(i). The coefficient a indicates how strongly this information propagates from one beat to the next. We are interested in the case where $0 \le a \le 1$.

Table 1. *Heart rate and fluctuation measures for subjects*

	Young ($n = 10$)	Old ($n = 10$)	Student's *t*-Test *P* Value
Mean heart rate	60.55 ± 8.77	57.22 ± 8.60	0.404
Range of heart rate	46–73	41–71	
SD heart rate	6.12 ± 1.28	2.82 ± 0.99	<0.001
Fluctuation measures			
α_s	0.90 ± 0.14	1.12 ± 0.19	0.009
α_l	0.99 ± 0.10	0.75 ± 0.17	0.002
β	1.14 ± 0.15	1.33 ± 0.29	0.101

Values are means ± SD; n = no. of subjects.

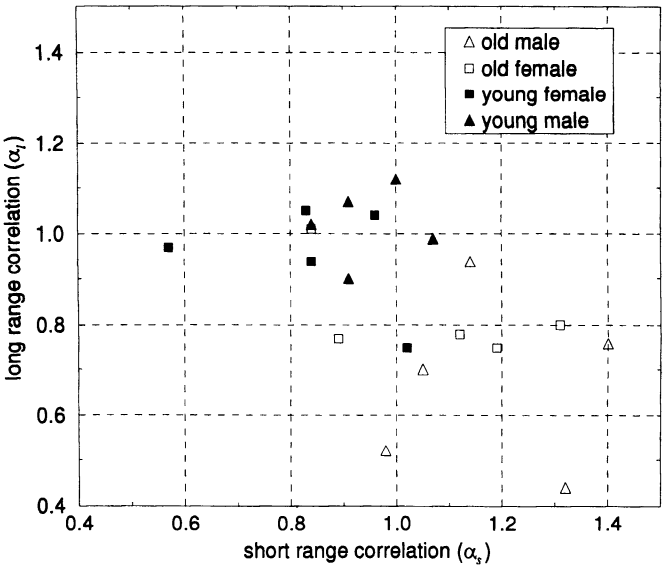

Fig. 3. Long-range vs. short-range correlation, quantified by α-exponent, for young and old, male and female subjects. Break points between the long- and short-range linear segments were chosen where local extrema occurred in the second derivative of the log-log fluctuation plot (Fig. 2*D*). Note the clustering of the young subjects near $\alpha_l = 1.0$ and the separation between young and old subjects.

There are several relevant points about this model. First, it is easy to show that

$$\text{R-R}(i+m) = a\text{R-R}(i+m-1) + \epsilon(i+m-1) = \cdots = a^m\text{R-R}(i) + \text{F}(\epsilon)$$

where m is an interval in time and F(ϵ) is a function of the stochastic variable ϵ and is therefore independent of R-R. Thus the correlation between R-R(i + m) and R-R(i) is proportional to $a^m = \exp(m \ln a)$. In other words, the autocorrelation function decays in an exponential way with a characteristic time scale $\tau = -1/\ln a$, because $a^m = \exp(m \ln a) = \exp(-m/\tau)$. We can also calculate the power spectrum [S(f)] of our model by a Fourier transform of the autocorrelation function. We obtain

$$\text{S}(f) = \frac{C\tau}{1 + (2\pi f\tau)^2}$$

where C is a constant.

Let us next consider two extreme cases of our model to get a better picture of the above calculation. *1*) Under

the condition $\alpha = 0$, there is no correlation between any two interbeat intervals; i.e., the R-R time series from this model will be white noise. Indeed, $\tau = -1/\ln 0 = -1/-\infty = 0$ and $S(f)$ is flat (equal to a constant). *2*) Under the opposite extreme condition, $\alpha = 1$, R-R time series behaves like a random walk (Brownian noise), with τ going to ∞ and $S(f)$ to $\sim 1/f^2$.

For α not equal to 0 or 1, $S(f)$ shows a crossover from Brownian noise for small time scales ($<\tau$), where the short-range correlation dominates the system, to white noise for large time scales ($>\tau$), where the noise (ϵ) in the system dominates the process. Note that this behavior is very similar to the interbeat interval time series of some of the elderly subjects.

Figure 4 shows a comparison between data from one elderly subject and our model simulation. We rescale the R-R time series to have zero mean and unit standard deviation, so the model has only one free parameter, α, to fit. The Fourier power spectrum and DFA plots confirm that the model can indeed mimic the fluctuations of interbeat interval in this elderly subject. Four elderly subjects, whose α_s ranged from 1.19 to 1.40 and α_1 from 0.44 to 0.80 (*bottom right* corner of Fig. 3), fit this model particularly well. Three of these subjects were the oldest in our sample (76, 77, and 81 yr), and the other was 71 years of age. There were no gender differences in our results (Fig. 3).

DISCUSSION

This study provides new information about age-related alterations in cardiovascular dynamics. We confirm previous observations in healthy young subjects (8, 18, 20, 22, 23) that cardiac interbeat intervals are neither random nor regular, but demonstrate fractal scaling, similar to those seen in many biological systems (1, 14). This is evident in the short- and long-term α-exponent values near 1, which is characteristic of $1/f$ noise.

Most importantly, our data suggest there may be a breakdown in the fractal scaling of interbeat interval fluctuations with healthy aging. In healthy elderly subjects as a group, there were two scaling regions in the interbeat interval time series, suggesting that processes influencing cardiac cycles over <40 beats differ from those that operate over the longer term. It is

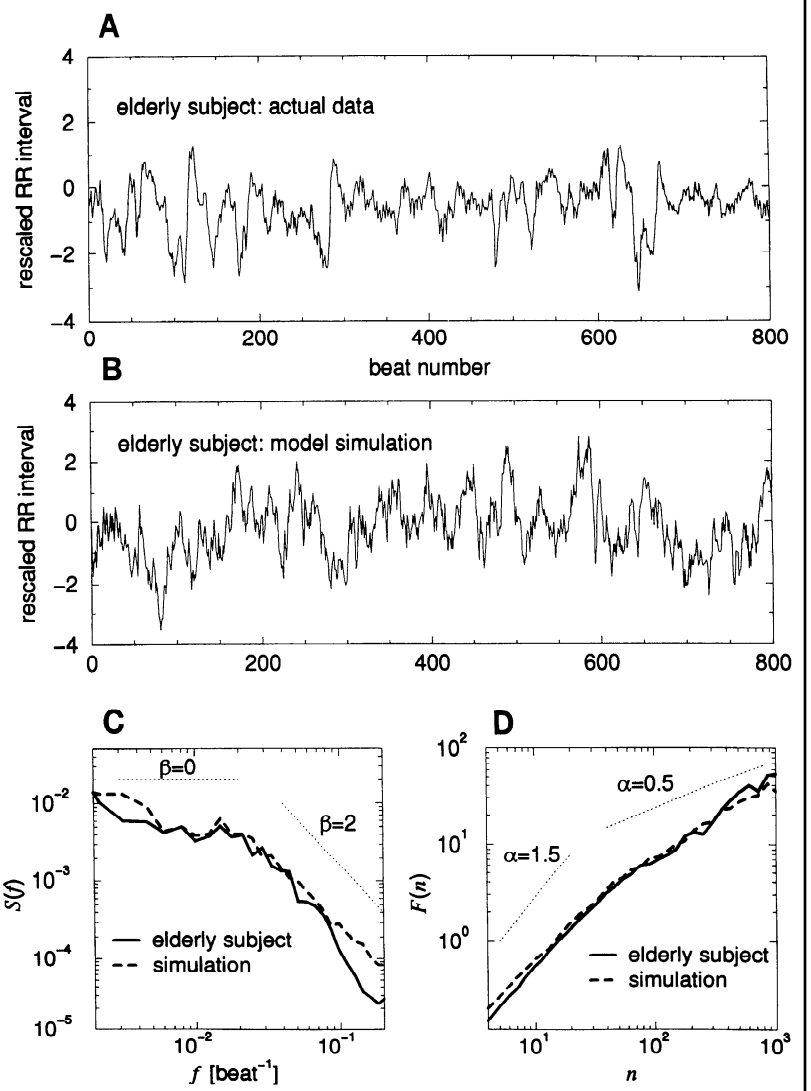

Fig. 4. R-R interval time series of a healthy 77-yr-old woman (*A*), simulated time series generated by a first-order autoregressive model (*B*), and the frequency spectrum [$S(f)$; *C*] and fluctuation plot (*D*) for the elderly subject (solid line) and model simulation (dashed line). Note the crossover behavior resulting in 2 scaling regions in the frequency spectra and fluctuation plots for both actual and simulated data. The model appears to fit the subject's data quite closely.

possible that short-term fluctuations in interbeat intervals represent primarily autonomic and respiratory influences, whereas longer-term physiological fluctuations are also due to endocrine systems, metabolic processes, volume shifts, and other influences. Over the short range in elderly subjects, interbeat interval fluctuations resembled a random walk process (Brownian noise), whereas over the longer range they resembled white noise. This apparent loss of fractal organization in heartbeat dynamics may reflect the degradation and decoupling of integrated physiological regulatory systems with aging.

Finally, we have shown that the dynamic heartbeat behavior of some elderly subjects (particularly the three oldest subjects located on the *bottom right* corner of the α_s vs. α_l relation shown in Fig. 3) fits a first-order autoregressive model. This model provides an explanation for the observed crossover behavior of the data from certain elderly subjects. For the healthy young subjects, less crossover was observed, as indicated by their position near the diagonal line $\alpha_s = \alpha_l$ in Fig. 3. This finding in the young implies a balance between many different physiological inputs that operate over different time scales to regulate cardiac cycle times. In contrast, if some of these inputs degrade and others dominate the system as a result of aging, crossover behavior may appear. In the autoregressive model discussed above, the interbeat intervals are strongly correlated over the short time scale, but then the correlation decays in an exponential fashion. This model suggests that one input with a characteristic time scale, τ, dominates the system.

There was large interindividual variability in the α-exponents and crossover behaviors of the elderly subjects. It is notable that three of the four subjects in whom the loss of fractal scaling was most marked were the oldest in our sample. This preliminary observation suggests that physiological aging may be associated with a progressive degradation in long-range interbeat interval correlations, which occurs at different rates in different individuals. Measures such as DFA that can quantify the dynamic properties of physiological systems may have application as biomarkers of physiological aging.

An age-related loss of fractal scaling in cardiovascular dynamics may impair an individual's ability to adapt to external and internal perturbations and predispose elderly people to the onset of disease (10, 12). This notion is supported by the previous observation that the development of presyncope during lower body negative pressure is associated with a reduction in the fractal dimension of heart rate variability (3). Furthermore, congestive heart failure is associated with a loss of long-range correlations in interbeat interval dynamics, with an average α_s value of 0.80 $\pm$ 0.26 (mean $\pm$ SD) and α_l value of 1.12 $\pm$ 0.22, both significantly different from values seen in normal subjects (17). Although aging may increase the risk of developing diseases like congestive heart failure, the age-related loss of fractal scaling is in an opposite direction, with a mean ($\pm$SD) α_s value of 1.12 $\pm$ 0.19 and α_l of 0.75 $\pm$ 0.17. The possibility that cardiac dynamics in healthy aging are distinct from those seen in heart disease opens new opportunities for the use of fluctuation measures as diagnostic tools to distinguish normal aging from occult disease. Further studies are needed in large groups of individuals with various ages and pathological conditions.

This study has several strengths as well as potential limitations. First, by using the new DFA technique and studying subjects under carefully controlled resting conditions, we have largely overcome the problem of distinguishing true physiological fluctuations from nonstationary environmental trends in time series data. Second, we have tried to ensure that our subjects are entirely healthy. On the basis of a rigorous screening protocol, including an exercise tolerance test, subjects were determined to be free of any detectable diseases, as well as medication use or toxic exposures that could influence the results. Although this increases our confidence that the findings represent changes solely attributable to physiological aging, the cross-sectional rather than longitudinal design of this study raises the possibility that our results may be due to cohort or other effects. The current study also did not address the physiological mechanisms underlying the changes in interbeat interval dynamics we observed.

Perspectives

The fractal organization of healthy sinus rhythm heartbeat dynamics is poorly understood but may represent a network of coupled neuronal pathways and feedback loops that regulates cardiac cycle time and thus permits rapid adaptation to physiological stress. Because vagal blockade with atropine sulfate appears to increase the β-exponent (i.e., reduce the fractal scaling) of resting R-R interval fluctuations in healthy humans; Ref. 23), the fractal nature of cardiac interval dynamics may be mediated in part by parasympathetic neural activity. Healthy aging is associated with a decline in vagal control of heart rate (5), as well as an impaired cardiac chronotropic response to β-adrenergic stimulation (9). Therefore, the observed age-related alterations in fractal scaling of interbeat interval dynamics may be partially due to degradation of autonomic nervous system influences. The loss of scale invariance and emergence of a dominant time scale in cardiac interbeat intervals of elderly subjects is consistent with this hypothesis. Additional studies are needed to determine the physiological mechanisms underlying the fractal nature of cardiac dynamics and how these change with aging and cardiovascular disease. Furthermore, if a loss of fractal scaling in the output of physiological control systems is associated with impaired adaptability or resiliency, measures such as DFA may be able to quantify individual disturbances in adaptive capacity and predict the onset of disease.

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