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Fractal scale-invariant and nonlinear properties of cardiac dynamics remain stable with advanced age: a new mechanistic picture of cardiac control in healthy elderly

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Schmitt DT, Ivanov PC. Fractal scale-invariant and nonlinear properties of cardiac dynamics remain stable with advanced age: a new mechanistic picture of cardiac control in healthy elderly. *Am J Physiol Regul Integr Comp Physiol* 293: R1923–R1937, 2007. First published August 1, 2007; doi:10.1152/ajpregu.00372.2007.—Heart beat fluctuations exhibit temporal structure with robust long-range correlations, fractal and nonlinear features, which have been found to break down with pathologic conditions, reflecting changes in the mechanism of neuroautonomic control. It has been hypothesized that these features change and even break down also with advanced age, suggesting fundamental alterations in cardiac control with aging. Here we test this hypothesis. We analyze heart beat interval recordings from the following two independent databases: *1*) 19 healthy young (average age 25.7 yr) and 16 healthy elderly subjects (average age 73.8 yr) during 2 h under resting conditions from the Fantasia database; and *2*) 29 healthy elderly subjects (average age 75.9 yr) during ≈8 h of sleep from the sleep heart health study (SHHS) database, and the same subjects recorded 5 yr later. We quantify: *1*) the average heart rate (<R-R>); *2*) the SD $\sigma_{R\text{-}R}$ and $\sigma_{\Delta R\text{-}R}$ of the heart beat intervals R-R and their increments ΔR-R; *3*) the long-range correlations in R-R as measured by the scaling exponent $\alpha_{R\text{-}R}$ using the Detrended Fluctuation Analysis; *4*) fractal linear and nonlinear properties as represented by the scaling exponents α^{sgn} and α^{mag} for the time series of the sign and magnitude of ΔR-R; and *5*) the nonlinear fractal dimension $D(k)$ of R-R using the fractal dimension analysis. We find: *1*) No significant difference in ($P > 0.05$); *2*) a significant difference in $\sigma_{R\text{-}R}$ and $\sigma_{\Delta R\text{-}R}$ for the Fantasia groups ($P < 10^{-4}$) but no significant change with age between the elderly SHHS groups ($P > 0.5$); and *3*) no significant change in the fractal measures $\alpha_{R\text{-}R}$ ($P > 0.15$), α^{sgn} ($P > 0.2$), α^{mag} ($P > 0.3$), and $D(k)$ with age. Our findings do not support the hypothesis that fractal linear and nonlinear characteristics of heart beat dynamics break down with advanced age in healthy subjects. Although our results indeed show a reduced SD of heart beat fluctuations with advanced age, the inherent temporal fractal and nonlinear organization of these fluctuations remains stable. This indicates that the coupled cascade of nonlinear feedback loops, which are believed to underlie cardiac neuroautonomic regulation, remains intact with advanced age.

aging; dynamics; heart rate; nervous system; autonomic; physiology; sleep; fractals; nonlinearity; scaling

THE OUTPUTS OF PHYSIOLOGICAL systems under neural regulation exhibit *1*) high degree of variability, *2*) spacial and temporal fractal organization that remains invariant at different scales of observation, and *3*) complex nonlinear properties (6, 46). These inherent features of physiological dynamics change significantly with different physiological states such as wake and sleep, exercise and rest, circadian rhythms, as well as with pathological conditions. Because different physiological states and pathological perturbations correspond to changes or even break down in the mechanism of the underlying neural regulation, alterations in certain dynamic properties of physiological signals have been found to be reliable markers of changes in physiological control.

Aging is traditionally associated with the process of decline of physiological function and reduction of physiological complexity (2, 35). One major hypothesis is that physiological aging results from a gradual change in the underlying mechanisms of physiological control (a regulatory network of neural and metabolic pathways interacting through coupled cascades of nonlinear feedback loops on a range of time and length scales), leading to changes of physiological dynamics. Under this hypothesis, even ostensibly healthy elderly subjects would exhibit: *1*) loss of sensitivity and decreased responsiveness to external and internal stimuli, leading to reduced physiological variability (2) and *2*) breakdown of certain feedback loops acting at different time scales in the regulatory mechanism of various physiological systems. This breakdown would lead to loss of physiological complexity as reflected in certain scale-invariant and nonlinear temporal characteristics of physiological dynamics (35, 41). This hypothesis of a breakdown of physiological complexity with healthy aging has recently been challenged (68). Furthermore, earlier studies have linked various pathological states with breakdown of the scale-invariant fractal organization in physiological dynamics, which is likely to result from disintegration of coupled feedback loops in the regulatory mechanism (15, 27, 28, 54, 61, 71). Thus, based on this hypothesis, mechanistically, physiological processes under healthy aging would be categorized in the same class as pathological dynamics where fractal organization and nonlinear complexity is lost.

A second hypothesis is that, while aging may lead to reduced variability, certain temporal fractal, scale-invariant and nonlinear structures embedded in physiological dynamics may remain unchanged. These two alternative hypotheses represent different notions about which aspects of the physiological control mechanisms are expected to change in the process of aging in contrast to the changes accompanying certain pathological conditions.

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To test these two hypotheses, we analyze cardiac dynamics, a typical example of an output of an integrated physiological system under autonomic neural regulation. Previous studies have shown that heart rate variability decreases with certain pathological conditions (46, 69) and with advanced age (51, 65). Studies based on approaches from statistical physics and nonlinear dynamics revealed that heart beat fluctuations in healthy subjects possess a self-similar fractal structure characterized by long-range power-law correlations over a range of time scales (37, 54, 61). The scaling exponent associated with these power-law correlations was shown to change significantly with rest and exercise (13, 36, 48), posture (66, 72), sleep and wake state (29), across sleep stages (8, 32, 33, 55) and circadian phases (23, 49), and to be a reliable marker of cardiac vulnerability under pathological conditions (21, 53). Furthermore, studies have found that turbulence-like multifractal and nonlinear features in heart beat dynamics are reduced and even lost with disease (25, 27, 39). Several studies have also reported reduced heart rate variability (67; as also shown in Fig. 1), apparent loss of fractal organization, as well as breakdown of scale-invariant correlations and certain nonlinear properties with advanced age (17, 18, 31, 41, 56), suggesting that healthy aging is associated with changes in the neuroautonomic mechanism of cardiac regulation related to disintegration of coupled feedback loops across a range of time scales.

Here, we investigate how cardiac dynamics change with advanced age by analyzing scale-invariant, linear, and nonlinear characteristics of heart beat fluctuations recorded from subjects during rest and sleep from two independent databases.

DATA AND METHODS

We analyze heart beat interval recordings from two independent databases.

Fantasia Database

The Fantasia database (15a) contains 20 young and 20 elderly subjects. We carefully selected 19 healthy young subjects (9 male; 10 female) with an average age of 25.7 yr (youngest 21; oldest 34) and 16 healthy elderly subjects (6 male; 10 female) with an average age 73.8 yr (youngest 68; oldest 85). All subjects were recorded while watching the movie Fantasia (Disney, 1940) in a relaxed supine or semirecumbent posture. These conditions were chosen to avoid the effect that differences in the level of physical activity between young and elderly subjects during daily routine might have on cardiac dynamics (Fig. 1). The continuous electrocardiogram (ECG) and respiration signals were digitized at 250 Hz. Each heart beat was annotated using the ARISTOTLE arrhythmia detector (50), and each beat annotation was verified by visual inspection. Only intervals between two normal beats were considered. One young and four elderly subjects (shown in Fig. 8) were excluded from our analysis because of artifacts in the data.

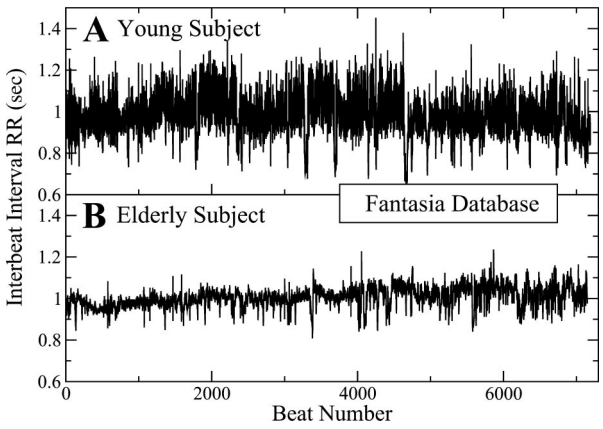

Fig. 1. Consecutive heart beat R-R intervals from a representative young healthy (*A*) and elderly (*B*) healthy subject from the Fantasia database. Under the same resting conditions elderly subjects exhibit significantly reduced heart rate variability.

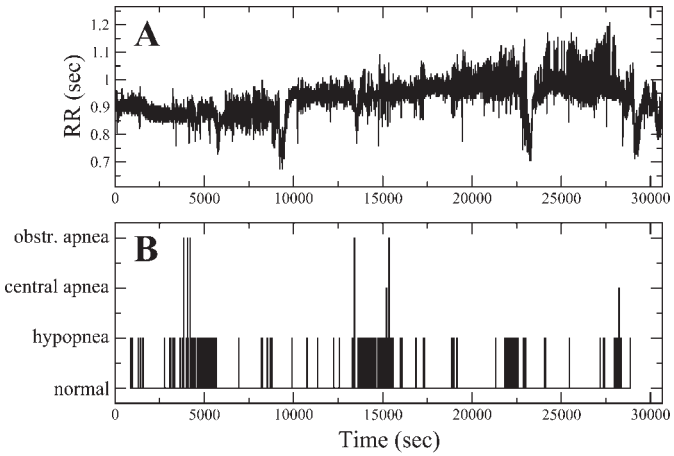

Fig. 2. Representative elderly subject from the Sleep Heart Health Study (SHHS) database. Consecutive heart beat R-R intervals (*A*) and apnea scoring (*B*).

Sleep Heart Health Study Database

The Sleep Heart Health Study (SHHS) is a prospective cohort study designed to investigate the relationship between sleep-disordered breathing and cardiovascular disease. Subjects were recorded during their habitual sleep periods of ≈8 h, and continuous ECG were recorded with 250 Hz (Fig. 2). Full details of the study design and cohort are provided in (40, 59). Details about obtaining the ECG and polysomnographic recordings are outlined (60). Sleep apnea episodes were annotated, and heart rate data during apnea (obstructive and central) were excluded from our analysis (Fig. 2). We selected a subset of 29 subjects (8 males; 21 females) with average age at the time of the first recording 75.9 yr (youngest 72; oldest 84). The recordings were repeated 5 yr later when the subjects were again screened and categorized as healthy.

Detrended Fluctuation Analysis

We use the detrended fluctuation analysis (DFA) method (52), which has been developed to quantify fractal correlations embedded in nonstationary signals, to estimate dynamic scale-invariant characteristics in heart beat fluctuations. Compared with traditional correlation analyzes such as autocorrelation, power-spectrum analysis, and Hurst analysis, the advantage of the DFA method is that it can accurately quantify the correlation property of signals masked by polynomial trends; it is described in detail in Refs. 9, 10, 22, 34, and 70.

The DFA method quantifies the detrended fluctuations $F(n)$ of a signal at different time scales n. A power-law functional form $F(n) \sim n^{\alpha}$ indicates the presence of self-similar organization in the fluctuations. The parameter α, called the scaling exponent, quantifies the correlation properties of the heart beat signal: if $\alpha = 0.5$, there is no correlation and the signal is white noise; if $\alpha = 1.5$, the signal is a random walk (Brownian motion); if $0.5 < \alpha < 1.5$, there are positive correlations, where large heart beat intervals are more likely

to be followed by large intervals (and the same is true for small heart beat intervals); if $\alpha < 0.5$ the signal is anticorrelated.

One advantage of the DFA method is that it can quantify signals with $\alpha > 1$, which cannot be done using the traditional autocorrelation and R/S analyses (14). In contrast to the conventional methods, the DFA method avoids spurious detection of apparent long-range correlations that are an artifact of nonstationary (63). Thus the DFA method is able to detect subtle temporal structures in highly heterogeneous physiological time series.

An inherent limitation of the DFA analysis is the maximum time scale $n_{\max}$ for which the fluctuation function $F(n)$ can be reliably calculated. To ensure sufficient statistics at large scales, it was shown that $n_{\max}$ should be chosen by $n_{\max} \leq N/6$, where N is the length of the signal (12, 22, 70). For time scales $n < n_{max}$ there is no bias in estimating the scaling exponent α. Thus recordings >1 h ($N \approx 3{,}600$ beats) are sufficient to reliably quantify α up to time scales $n = 600$ beats, and differences in the length of the recordings between the Fantasia database (2 h) and SHHS database (8 h) do not affect the estimate of α. Recent studies have tested the performance of the DFA method when applied to correlated signals with patches of missing data, random spikes, and superposed trends related to different activity levels and patches with different standard deviation and local correlations, as often found in heart beat data (10, 22).

Both the Fantasia database and the National Institutes of Health SHHS database have used 250-Hz sampling rate for the ECG recordings. A precision of 0.004 s (250 Hz) is more than sufficient for our analysis, since the DFA method as well as the magnitude and sign analyses (MSA) and fractal dimension analysis (FDA) analyses we employ (see below) are robust in that respect. Use of a lower sampling rate (i.e., lower precision in the estimate of the R-R intervals) acts effectively as added random noise with an amplitude proportional to the sampling interval; in our case, the amplitude of this sampling noise is more than two orders of magnitude smaller than the R-R interval. It has been shown that adding noise with such a small amplitude to a fractal correlated signal does not effect the correlation scaling and fractal properties (10).

MSA

Because the DFA method quantifies linear fractal characteristics related to two-point correlations, we have selected the MSA method to probe for long-term nonlinear properties in the data. Specifically, it has been shown that signals with identical temporal organization, quantified by the DFA-scaling exponent α, can exhibit very different nonlinear properties captured by the MSA method (5).

The MSA method (3, 4) consists of the following steps: *1*) given R-R_i series we obtain the increment series, $\Delta\text{R-R}_i = \text{R-R}_{i+1} - \text{R-R}_i$; *2*) we decompose the increment series into a magnitude series ΔR-R and a sign series (ΔR-R); *3*) to avoid artificial trends, we subtract the average from the magnitude series; *4*) because of limitations in the accuracy of the DFA method for estimating the scaling exponents of anticorrelated signals ($\alpha < 0.5$), we integrate the magnitude series (22); *5*) we perform a scaling analysis using DFA; and *6*) to obtain the scaling exponents for the magnitude series, we measure the slope of $F(n)/n$ on a log-log plot, where $F(n)$ is the fluctuation function and n is the time scale of analysis.

This approach is sensitive to nonlinear features in signals (64). We find that positive correlations in the magnitude series ($\alpha_{\text{mag}} > 0.5$) are a reliable marker of long-term nonlinear properties. Thus we employ the MSA as a complementary method to the DFA, because it can distinguish physiological signals with identical long-range correlations, as quantified by the DFA method, but with different nonlinear properties and different temporal organization for the sign(ΔR-R) series.

FDA

The fractal dimension $D(k)$ is a local nonlinear measure used to quantify the irregularity of a time series (47). We estimate the fractal dimension using an algorithm proposed previously (19).

Starting from a discrete time series, $x(i)$, with $i \in [1,N]$, a new sparse time series x_k^m is constructed in the following way

$$x_k^m;\ x(m),\ x(m+k),\ \ldots,\ x\left(m + \left\lfloor \frac{N-m}{k} \right\rfloor k\right), \qquad (1)$$

with $m \in [1,k]$ where m and k are integers, and $\lfloor (N-m)/k \rfloor$ denotes the largest integer number smaller than $(N-m)/k$. Then a length measure for this sparse time series is defined as

$$L_m(k) = \frac{N-1}{hk^2}\left(\sum_{i=1}^{h} \left|x_{ik}^m - x_{(i-1)k}^m\right|\right), \qquad (2)$$

with $h \equiv \lfloor (N-m)/k \rfloor$. For a time series $x(i)$ with a fractal dimension D the length $L_m(k)$ averaged over m is a power-law function of the scale k: $L(k) \equiv \langle L(k) \rangle_m \sim k^{-D}$. In the general case D can depend on the scale k. In this case, the local fractal dimension $D(k)$ of the time series $x(i)$ is defined as the negative local derivative of log $L(k)$ as a function of log k (Table 1).

RESULTS

Variability in Heart Beat Intervals and Their Increments

We first test the possibility that advanced age in ostensibly healthy subjects would lead to an increase in the average heart rate and to a significant reduction in heart rate variability, a behavior previously observed in subjects with congestive heart failure where under suppressed vagal tone increased heart rate is associated with reduced heart rate variability (69, 71). We find that both young and elderly healthy subjects in the Fantasia database exhibit very similar group average interbeat intervals: $\langle\text{R-R}\rangle \pm \sigma = 0.9 \pm 0.14$ for the young group and $\langle\text{R-R}\rangle \pm \sigma = 1.06 \pm 0.17$ for the elderly group, where σ is the standard deviation (Table 2). This is in agreement with

Table 1. *Overview of measures used*

Abbreviation	Measure	Significance
	Static measures	
$\langle\text{R-R}\rangle$ (AVNN)	Mean of R-R intervals	Inversely proportional to heart rate
$\sigma_{\text{R-R}}$ (SDNN)	SD of R-R	Para- and sympathetic HRV measure sensitive to trends
$\sigma_{\Delta\text{R-R}}$ (RMSSD)	SD of ΔR-R	Parasympathetic HRV measure insensitive to trends
	Dynamic measures	
α	Scaling exponent of R-R	Linear scale-invariant correlations
α^{mag}	Scaling exponent of $\lvert\Delta\text{R-R}\rvert$	Nonlinear scale-invariant correlations
α_1^{sgn}	Scaling exponent of sgn(ΔR-R)	Fractal measure of directionality
$D(k)$	Fractal dimension of R-R	Nonlinear fractal measure

Table 2. *Average values and SD of <R-R>, $\sigma_{R\text{-}R}$ (SDNN), $\sigma_{\Delta R\text{-}R}$ (RMSSD), and DFA-2 scaling exponents for subjects from the Fantasia database and the SHHS database*

	Fantasia Database			SHHS Database		
Measure	Young	Elderly	*P* Value	Elderly	Elderly + 5 yr	*P* Value
<R-R>	0.9±0.14	1.06±0.17	0.11	0.92±0.08	0.92±0.1	0.92
$\sigma_{R\text{-}R}$	0.089±0.034	0.051±0.017	**3.3×10^{-4}**	0.077±0.027	0.081±0.024	0.50
$\sigma_{\Delta R\text{-}R}$	0.061±0.031	0.027±0.012	**9.9×10^{-5}**	0.028±0.015	0.028±0.013	0.74
α_1	1.09±0.24	1.22±0.29	0.16	1.12±0.27	1.09±0.28	0.78
α_2	0.76±0.08	0.78±0.12	0.47	0.88±0.12	0.97±0.12	0.01
α_1^{mag}	0.53±0.1	0.56±0.08	0.36	0.57±0.13	0.60±0.13	0.49
α_2^{mag}	0.64±0.11	0.68±0.11	0.45	0.70±0.12	0.72±0.13	0.58
α_1^{sgn}	0.24±0.15	0.3±0.2	0.28	0.23±0.19	0.21±0.19	0.74
α_2^{sgn}	0.47±0.09	0.44±0.08	0.37	0.38±0.07	0.39±0.07	0.77

Data are averages ± SD. AVNN, average normal to normal heartbeat interval; SDNN, SD of normal to normal heartbeat interval; RMSSD, root mean square SD of normal to normal heartbeat interval. For the Fantasia database, detrended fluctuation at the time scale $n \in F(n)$] was fitted in the interval $n \in [6,16]$ for α_1 and $n \in [60,(N/6)]$ for α_2. For the Sleep Heart Health Study (SHHS) database, $F(n)$ was fitted in the interval n ∈ [6,16] for α_1 and n ∈ [60,600] for α_2. A two-tailed Student's *t*-test was performed to obtain the *P* values. *P* values that indicate significant differences between young and elderly groups are shown in bold.

previous studies (11, 31, 56). A Student's *t*-test shows no significant difference between the two groups with a *P* value = 0.11. A very similar average heart beat interval was observed for the healthy elderly subjects in the SHHS database with $<\text{R-R}> \pm \sigma = 0.92 \pm 0.075$, indicating no significant difference (*P* value = 0.07) compared with the group of young Fantasia subjects (Table 2). Furthermore, comparing the group average heart beat interval of the elderly subjects from the SHHS database with the same subjects recorded 5 yr later, we find again no significant difference: $<\text{R-R}> \pm \sigma = 0.92 \pm 0.08$ at the first recording and $<\text{R-R}> \pm \sigma = 0.92 \pm 0.1$ after 5 yr (*P* value = 0.92; Table 2). Thus we do not observe a significant change in the average heart rate with advanced age.

To test whether there is a reduction in heart rate variability with aging, we next estimate for each subject the standard deviation of the heart beat intervals $\sigma_{R\text{-}R}$ (often denoted as SDNN) and the standard deviation of the increments in the consecutive heart beat intervals $\sigma_{\Delta R\text{-}R}$ (often denoted as RMSSD) (Table 2). For the young and elderly subjects in the Fantasia database, we find a statistically significant difference with *1*) a higher value for the group average $<\sigma_{R\text{-}R}>$ and *2*) larger inter-subject variability for the young group: $<\sigma_{R\text{-}R}> \pm \sigma = 0.089 \pm 0.034$ for the young compared with $<\sigma_{R\text{-}R}> \pm \sigma = 0.051 \pm 0.017$ for the elderly subjects (*P* value = 3.3×10^{-4}; Table 2). Similarly, we observe a significantly higher value for the group average $<\sigma_{\Delta R\text{-}R}>$ for the young subjects in the Fantasia database ($<\sigma_{\Delta R\text{-}R}> \pm \sigma = 0.061 \pm 0.031$) compared with the elderly subjects ($<\sigma_{\Delta R\text{-}R}> \pm \sigma = 0.027 \pm 0.012$; *P* value = 9.9×10^{-5}), again with a larger intersubject variability for the young group (Table 2). We note that the sampling rate of 250 Hz does not effect the significance of the difference in $\sigma_{\Delta R\text{-}R}$ between the young and elderly groups, since this difference is ~0.034 s, i.e., one magnitude larger than the sampling precision of 0.004 s.

For the group of healthy elderly subjects from the SHHS database, we find a higher value of $<\sigma_{R\text{-}R}> \pm \sigma = 0.077 \pm 0.027$ compared with the elderly group from the Fantasia database, a difference that could be attributed to the fact that the SHHS subjects were recorded during sleep where transitions between sleep stages are associated with trends and larger fluctuations in the interbeat interval time series (32, 55), whereas the elderly Fantasia subjects were recorded during rest. In contrast, for $<\sigma_{\Delta R\text{-}R}>$, we do not observe a significant difference between the elderly groups from the Fantasia and SHHS database (*P* value = 0.74; Table 2). However, we find a significant difference between young and elderly subjects, indicating a clear reduction in the heart rate variability with aging.

Fractal Correlations

We next test whether the temporal organization in the heart beat fluctuations changes in ostensibly healthy elderly compared with young subjects. Earlier studies have shown that heart beat fluctuations exhibit self-similar power-law correlations over a broad range of time scales ranging from seconds to many hours (37, 62) and that the scaling exponents associated with these power-law correlations change significantly with sleep and wake state (29) and with pathological conditions (53, 54), reflecting changes in the underlying mechanism of cardiac regulation. Specifically, heart beat fluctuations of healthy subjects during daily activity exhibit 1/*f*-like power spectrum (37, 54, 61) with a scaling exponent $\alpha \approx 1$ (see DATA AND METHODS). During sleep, this behavior changes to exponent $\alpha \approx 0.8$ at time scales >60 beats, indicating stronger anticorrelations in the interbeat increments ΔR-R during sleep compared with the wake state (29 and Fig. 3*A*). In contrast, for pathological conditions such as congestive heart failure, earlier studies have reported a value for the exponent α closer to 1.5, which is typical for random walk behavior (Brownian motion) and associated with loss of cardiac control (53).

Applying the DFA method, we obtain a very similar scaling behavior for a representative healthy young and a healthy elderly subject from the Fantasia database, both characterized by a scaling exponent $\alpha_2 \approx 0.8$ at intermediate and large time scales (Fig. 3, *B* and *C*). At small time scales for both representative subjects, we observe a crossover to a higher exponent of $\alpha_1 \approx 1.1$ (Fig. 3, *B* and *C*). Although there is certain intersubject variability in the scaling functions $F(n)$, this crossover behavior remains robust with a group average scaling exponent $\alpha_1 \approx 1.1$ at small scales and $\alpha_2 \approx 0.75$ at large scales for the young subjects, and, respectively, $\alpha_1 \approx 1.2$ and $\alpha_2 \approx 0.8$ for the elderly subjects (see APPENDIX and Fig. 12). Our analysis indicates no significant difference in the scaling behavior between healthy young and healthy elderly subjects

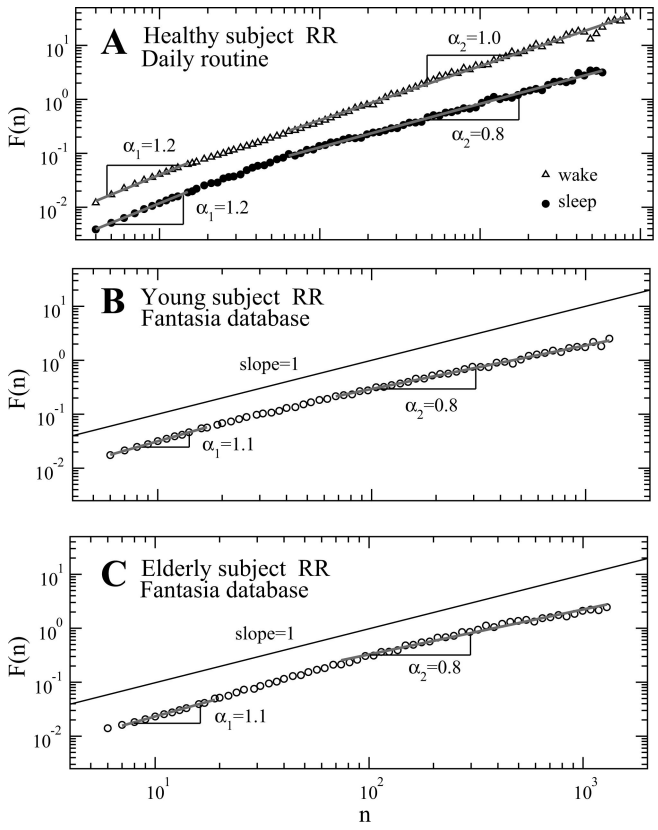

Fig. 3. Fluctuation function $F(n)$ vs. time scale n (in heart beat number) obtained using DFA-2 for 6 h-long record of R-R heart beat intervals during wake and sleep from a representative healthy subject [MIT-BIH Normal Sinus Rhythm Database (15a); *A*], as well as 2 h-long records of a representative healthy young subject (*B*) and healthy elderly subject (*C*) from the Fantasia database. A very similar scaling behavior is observed for the representative young (*B*) and elderly (*C*) subjects that closely resembles the scaling behavior of the healthy subjects during sleep shown in *A* [MIT-BIH Normal Sinus Rhythm Database (15a)], indicating no *change* in the scale-invariant temporal correlations of heart beat intervals with advanced age under healthy resting conditions. Scaling curves for all individuals are shown in APPENDIX and Fig. 12.

under the resting conditions in the Fantasia study protocol (Table 2). We note that our findings for the young and elderly Fantasia subjects (Fig. 3, *B* and *C*) are very similar to the scaling behavior in heart beat fluctuations previously reported for healthy subjects during sleep (29), which exhibit a crossover from $\alpha_1 \approx 1.2$ at small time scales to $\alpha_2 \approx 0.8$ at intermediate and large time scales (Fig. 3*A*). This similarity in the scaling properties of heart beat dynamics of healthy subjects during sleep (Fig. 3*A*) and the Fantasia database subjects (Fig. 3, *B* and *C*) may be attributed to the fact that, under the Fantasia study protocol, subjects are resting in a semirecumbent/supine posture, watching a relaxing movie, physiological conditions that more closely resemble sleep than daytime activity.

To confirm the validity of these findings, we further investigate the scale-invariant correlation properties of cardiac dynamics for healthy elderly subjects from the SHHS database, where heart rate data were recorded during sleep, a protocol that differs from the Fantasia study (see DATA AND METHODS). In Fig. 4, we show the DFA scaling curves for a representative SHHS subject with a crossover in the scaling behavior from $\alpha_1 \approx 1.1$ at small time scales to $\alpha_2 \approx 0.9$ above 60 beats. This scaling behavior is very similar to the one we find for both young and elderly subjects from the Fantasia database (Fig. 3). Furthermore, comparing the scaling behavior of the elderly subjects from the SHHS database with the same subjects recorded five years later, we do not find a significant difference in the correlation scaling exponents α_1 and α_2 (Fig. 4 and Table 2). The results shown in Figs. 3 and 4, the APPENDIX, and Fig. 12 indicate that the fractal correlation properties of healthy heart beat dynamics remain stable and do not significantly change with advanced age.

MSA

Recent studies have demonstrated that scale-invariant processes with identical long-range power-law correlations may be characterized by very different dynamics for the magnitude and sign of their fluctuations (5, 32) and that the information contained in the temporal organization of the magnitude and the sign time series is independent from the correlation properties of the original time series (3). Specifically, for cardiac dynamics of healthy subjects, it was shown (5) that heart beat intervals during routine daily activity exhibit correlation properties at intermediate and large time scales characterized by scaling exponent $\alpha_2 \approx 1$ while at the same time scales the magnitude series of the increments in consecutive heart beat intervals is characterized by $\alpha_2^{mag} \approx 0.8$. Furthermore, although correlations reflect the linear properties of heart beat dynamics, the temporal structure of the magnitude of interbeat increments has been shown to relate to the nonlinear properties encoded in the Fourier phases (3, 5, 64). For certain pathological conditions such as congestive heart failure, previous studies have reported loss of nonlinearity (57) associated with a breakdown of the multifractal spectrum (25), and reduced scaling exponent α_{mag} for the magnitude series (3).

For the magnitude time series of the interbeat increments, we obtain $\alpha_1^{mag} \approx 0.53$ at small time scales and $\alpha_2^{mag} \approx 0.68$ at intermediate and large time scales for a representative young subject (Fig. 5*A*) and very similar results with $\alpha_1^{mag} \approx 0.53$ and

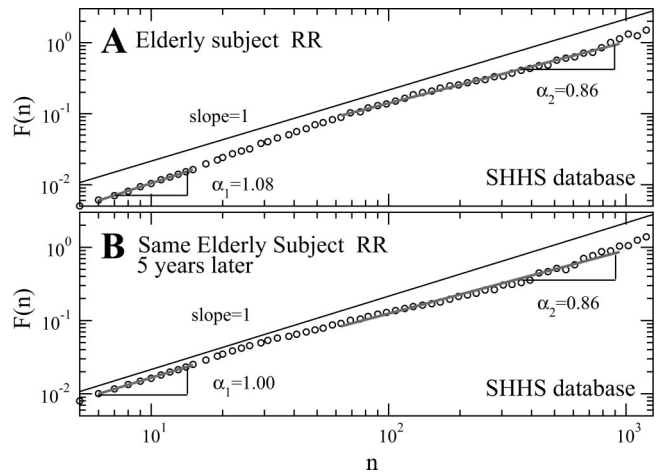

Fig. 4. Fluctuation function $F(n)$ vs. time scale n (in heart beat number) obtained from detrended fluctuation analysis (DFA)-2 for ≈8-h long records of R-R heart beat intervals during sleep for representative healthy elderly subject from the SHHS database (*A*) and the same elderly subject 5 yr later (*B*). The very similar values for the exponents α_1 and α_2 indicate no breakdown of linear fractal correlations with advanced age under healthy conditions. Note the similarity with the scaling behavior for the young subjects, shown in Fig. 3, the APPENDIX, and Fig. 12, which is not consistent with the hypothesis of a gradual loss of scale-invariant complexity in the process of aging.

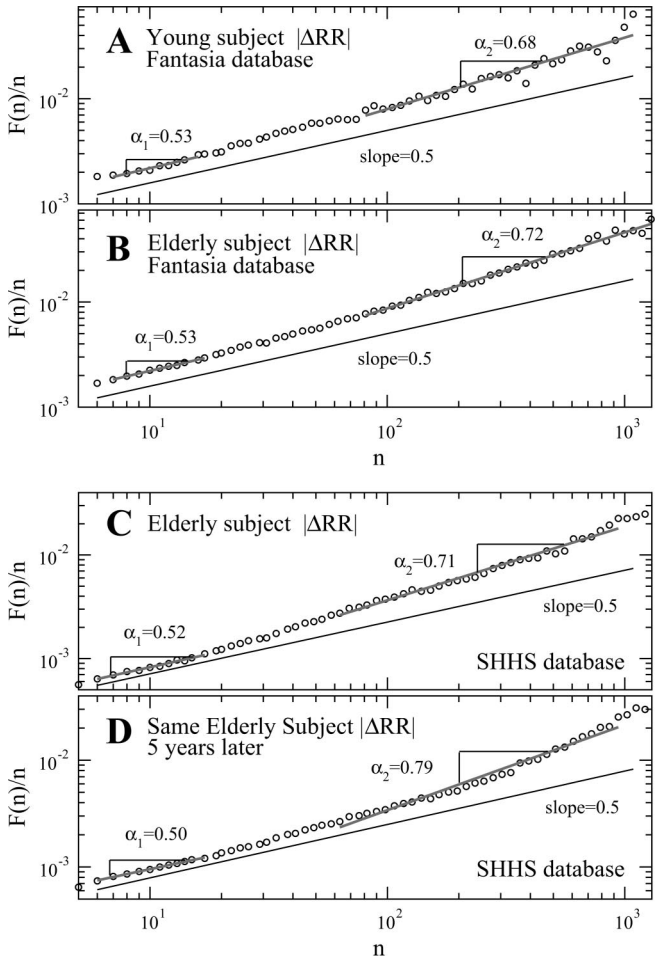

Fig. 5. Fluctuation function $F(n)$ vs. time scale n (in beat number) obtained for the magnitude of the interbeat increments (ΔR-R) using DFA-2 for a representative healthy young (*A*) and healthy elderly (*B*) subject from the Fantasia database, and for a representative healthy elderly subject from the SHHS database (*C*) and the same subject recorded 5 yr later (*D*). All subjects exhibit a very similar scaling behavior characterized by an exponent $\alpha_2^{mag} \approx 0.7$ at intermediate and large time scales, very different from $\alpha_{mag} = 0.5$ characteristic for linear processes with no correlations in the Fourier phases (3, 5), which indicates that the long-term nonlinear properties of heart beat dynamics do not break down with advanced age under healthy resting conditions. This is in contrast to the hypothesis linking the process of healthy aging with a gradual loss of nonlinearity. Scaling curves for all individuals from the Fantasia database are shown in the APPENDIX and Fig. 13.

$\alpha_2^{mag} \approx 0.72$ for a representative elderly subject from the Fantasia database (Fig. 5*B*). The DFA scaling functions $F(n)$ for all young and elderly subjects, shown in APPENDIX and Fig. 13, exhibit a consistent behavior among the subjects in each group with a smooth crossover from a group average magnitude exponent $\alpha_1^{mag} \approx 0.53$ at small and intermediate time scales to $\alpha_2^{mag} \approx 0.64$ at large scales for the young group, and a similar crossover from a group average exponent $\alpha_1^{mag} \approx 0.6$ at small and intermediate time scales to $\alpha_2^{mag} \approx 0.7$ at large scales for the elderly group (Table 2).

To confirm these findings, we next calculate the magnitude scaling exponent of the interbeat increments for the elderly subjects from the SHHS database. Again we observe a crossover from $\alpha_1^{mag} \approx 0.52$ at small scales to $\alpha_2^{mag} \approx 0.7$ at large time scales shown in Fig. 5*C* for a representative elderly subject, a behavior very similar to the one observed for both young and elderly Fantasia subjects shown in Fig. 5, *A* and *B*. Our analysis does not show a statistically significant difference in the group average magnitude scaling exponents α_1^{mag} (with P value = 0.71) and α_2^{mag} (with P value = 0.57) between the elderly SHHS subjects and the elderly Fantasia subjects. Moreover, we find no significant difference in α_1^{mag} (with P value = 0.24) and α_2^{mag} (with P value = 0.16) between the elderly SHHS subjects and the young Fantasia subjects.

For the sign of the interbeat increments time series, we again find no significant difference in the scaling behavior between the young and elderly subjects in the Fantasia database with practically identical exponents of $\alpha_1^{sgn} \approx 0.2$ at short time scales and $\alpha_2^{sgn} \approx 0.4$ at intermediate and large time scales (Fig. 6, *A* and *B*). We observed a consistently similar behavior for all subjects in the young and elderly group in the Fantasia database (APPENDIX and Fig. 14), where the scaling function $F(n)$ exhibits a crossover from strongly anticorrelated behavior at

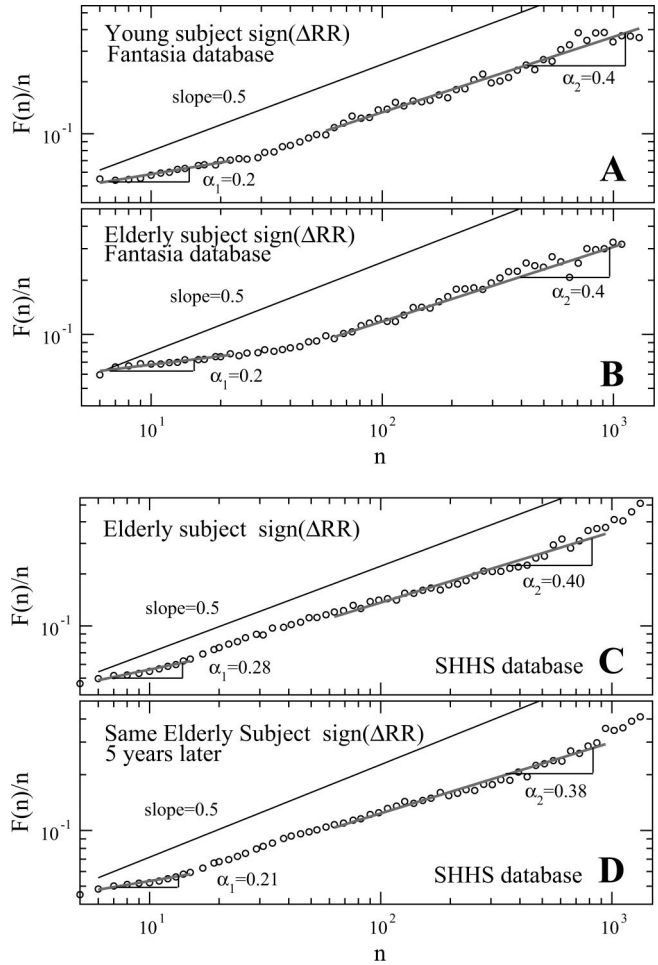

Fig. 6. Fluctuation function $F(n)$ vs. time scale n (in beat number) obtained for the sign of the interbeat increments [sign(ΔR-R)] using DFA-2 for a representative healthy young (*A*) and healthy elderly subject (*B*) in the Fantasia database, and for representative healthy elderly subject from the SHHS database (*C*) and the same elderly SHHS subject recorded 5 yr later (*D*). All subjects exhibit a very similar scaling behavior for the sign with a crossover from strong anticorrelations with $\alpha_1^{sgn} \approx 0.2$ at small time scales to weaker anticorrelations with $\alpha_2^{sgn} \approx 0.4$ at large scales, indicating a similar fractal organization of sympathetic and parasympathetic control in both young and elderly subjects under healthy resting conditions. Scaling curves for all individuals in the Fantasia database are shown in the APPENDIX and Fig. 14.

short time scales to weaker anticorrelations at larger scales, respectively, characterized by group average sign exponents $\alpha_1^{sgn} \approx 0.24$ for the young and $\alpha_1^{sgn} \approx 0.3$ for the elderly subjects at small scales and $\alpha_2^{sgn} \approx 0.47$ for the young and $\alpha_2^{sgn} \approx 0.43$ for the elderly subjects at large scales. These results indicate no significant difference in the temporal organization of the sign series between the young and the elderly subjects in the Fantasia database (Table 2).

Repeating our sign scaling analysis for the SHHS database, we observe a crossover from strongly anticorrelated behavior with an exponent $\alpha_1^{sgn} \approx 0.2$ at small time scales to weaker anticorrelations with $\alpha_2^{sgn} \approx 0.4$ at intermediate and large time scales, as shown in Fig. 6, *C* and *D*. This crossover behavior is very similar to the one we find for both young and elderly Fantasia subjects (Fig. 6, *A* and *B*, APPENDIX, and Fig. 14). Moreover, we do not find a significant difference in the scaling of the sign series for the elderly SHHS subjects and the same subjects 5 yr later (Fig. 6, *C* and *D* and Table 2).

FDA

Finally, we employ the FDA method (see DATA AND METHODS) to estimate the fractal dimension $D(k)$ of a time series (14, 19, 47). It has been demonstrated that the fractal dimension is a measure that represents the nonlinear properties in the output of a dynamical system so that two signals with identical scale-invariant correlations may be quantified by different fractal dimension depending on the degree of nonlinearity encoded in the Fourier phases (20, 64). Our analysis shows no significant difference in the group average of the nonlinear fractal dimension measure $D(k)$ between the young and the elderly subjects in the Fantasia database for the whole range of time scales except for a very short time interval of six to eight heart beats (Fig. 7*A*), which are time scales typical for sleep apnea (see Fig. 8). At smaller and larger time scales, the average fractal dimension $D(k)$ converges for both groups (Fig. 7*A*). Furthermore, we do not observe a statistically significant difference between the elderly subjects from the SHHS database and the same subjects recorded 5 yr later (Fig. 7*B*). These findings do not support the hypothesis that nonlinearity is reduced in healthy elderly subjects.

Summary of the Results

In agreement with previous studies (11, 31, 56, 65), we observe a certain degree of reduction in heart rate variability, as measured by $\sigma_{R\text{-}R}$ (SDNN) and $\sigma_{\Delta R\text{-}R}$ (RMSSD), when comparing young with elderly subjects (Table 2). In contrast to previous studies (31, 41, 56), however, we do not find a significant difference in the scaling exponents α_1 and α_2 characterizing the fractal scale-invariant temporal organization of heart beat fluctuations between young and elderly subjects (Table 2). For the scaling properties of the magnitude and the sign of heart beat fluctuations, which have been shown to carry additional independent information about the nonlinear and linear properties of a time series (3, 5, 32), we find that these measures also remain unchanged when comparing young and healthy elderly subjects (Table 2). Finally, for the fractal dimension $D(k)$ of the heart beat interval time series, an independent nonlinear measure, again contrary to previous reports (18), we do not find significant differences between young and elderly subjects. Furthermore, comparing longitudinal data from a group of elderly subjects who were also recorded 5 yr later, we find that the heart rate variability is not further reduced (Table 2) and that the scaling exponents α_1 and α_2 of the heart beat fluctuations, as well as the nonlinear features as measured by the magnitude exponent α_{mag} and the fractal dimension $D(k)$, remain stable.

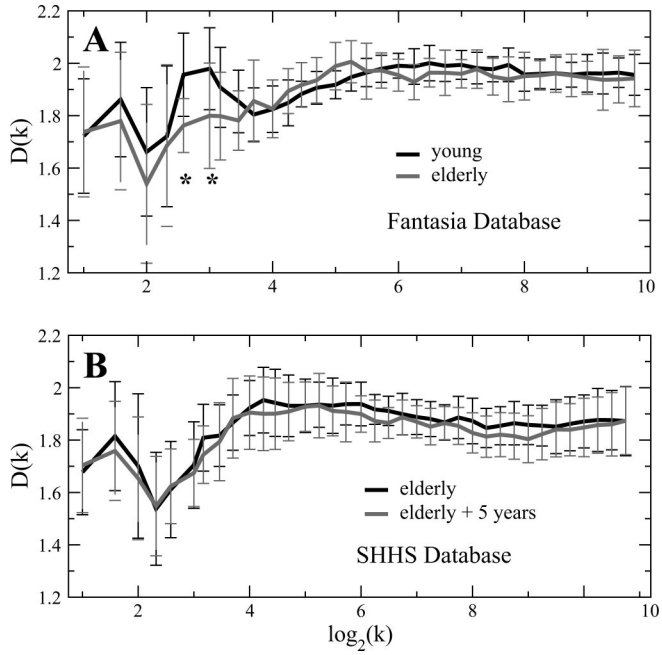

Fig. 7. Group average nonlinear fractal dimension $D(k)$ vs. time scale $\log_2 k$, where k is measured in beat numbers for young and elderly healthy Fantasia subjects (*A*) and healthy elderly SHHS subjects and the same subjects 5 yr later (*B*). There is no significant difference in the group averages indicated by the overlapping SDs except for the interval of scales $k \in [3,6]$ marked by * in *A* (P value $= 1.94 \times 10^{-4}$ and 6×10^{-3} correspondingly). Note the very similar profile of $D(k)$ for all groups, indicating no apparent loss of nonlinearity with aging, in agreement with our findings for the long-term nonlinear properties represented by the magnitude exponent α_2^{mag} shown in Fig. 5.

These findings indicate that, in the process of aging, the alterations in the underlying mechanisms of cardiac autonomic regulation are not likely to involve breakdown of coupling between feedback loops at different time scales or dominance of a particular feedback loop at a given time scale, as often observed with pathological perturbations (21, 26, 30, 38, 42, 44). Rather, our findings suggest a reduced reflexiveness of the neuroautonomic regulation with aging while the nonlinear feedback interactions across time scales between elements of the cardiac regulatory system remain unchanged.

INTERPRETATION AND MODELING

Our findings indicate that scale-invariant correlation and nonlinear properties do not significantly change in healthy elderly subjects compared with young subjects. This is in contrast to some earlier studies, based on the same Fantasia database (or on a subset of it), which have reported loss of fractal organization in heart beat fluctuations, a behavior resembling Brownian motion (random walk process) with $\alpha = 1.5$ at small scales and white noise with $\alpha = 0.5$ over large scales (31, 56), as well as a significant loss of nonlinearity (18) with healthy aging. A possible reason for these different findings may be the presence of artifacts in the data such as

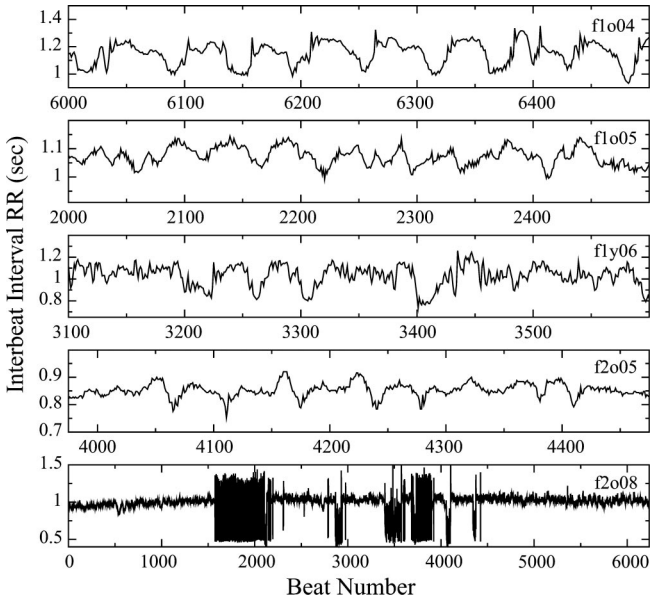

Fig. 8. Recordings of heart beat intervals from one young and four elderly subjects in the Fantasia database excluded from our analysis. The first four recordings contain many segments with well-pronounced periodic patterns, the period and amplitude of which are typical for sleep apnea (see Fig. 9). The last recording contains segments of corrupted data. These artifacts strongly influence scaling and fractal and nonlinear measures (see Figs. 10 and 11) and can lead to spurious differences between young and elderly subjects.

segments of corrupted recordings or certain periodic patterns (Fig. 8). These periodic patterns strongly resemble episodes of sleep apnea, as shown in Fig. 9*A*. Indeed, sleep apnea may be present in the elderly subjects from the Fantasia database, since they have not been specifically screened for sleep apnea. Furthermore, ECG recordings were taken when subjects were watching a calming movie for 2 h in a semirecumbent or supine posture during which subjects may have fallen asleep for periods of time, when apnea episodes are likely to occur.

The periodic patterns we observe in wide segments of the interbeat interval recordings shown in Figs. 8 and 9*A* have a period of ~30 to 60 s, typical for apnea episodes (Fig. 9*B* and Refs. 26, 30, and 58). Similar apnea-like patterns are also present in the breathing records of some Fantasia subjects (Figs. 8 and 9*A*). These periodic patterns have a very strong effect on the scaling analysis, as shown in earlier studies (22), leading to a pronounced crossover at the time scale corresponding to the period of the patterns. This crossover separates a regime of apparent Brownian-motion-type behavior with $\alpha \approx 1.5$ at smaller scales from a second regime of apparent white noise behavior $\alpha \approx 0.5$ at larger scales (Figs. 10*F* and 11), a behavior that in earlier studies (31, 56) has been spuriously attributed to changes in the cardiac neuroautonomic control due to aging.

To model the effect that periodic patterns of sleep apnea have on the scaling properties of heart beat intervals, we first generate a fractal correlated signal X_η using the Makse et al. (45) algorithm. To account for the statistical properties observed in heart beat intervals, we rescale the signal to have the mean value $<X_\eta(i)> = 1$, standard deviation $\sigma_{X\eta} = 0.05$, and correlation scaling exponent $\alpha_{X\eta} = 0.8$ (Fig. 10*A*), which match the group mean <R-R>, standard deviation $<\sigma_{R\text{-}R}>$ (Table 2), and scaling exponent value $<\alpha_2>$ (APPENDIX and Fig. 12, *C* and *D*) of the elderly subjects in the Fantasia database. To model the periodic influence of sleep apnea on the heart beat intervals, we generate a sinusoidal signal, $X_s(i) = A \sin(2\pi i/T)$, with a period $T = 50$ (similar to the average period of 50 heart beats in apnea patterns) and amplitude $A = 0.1$ (as observed in apnea patterns; Fig. 10*B*), and we superpose the sinusoidal signal X_s with the fractal correlated signal $X_\eta(i)$ to obtain $X_{\eta s}(i) = X_\eta(i) + X_s(i)$ (Fig. 10*C*). We note that $X_{\eta s}(i)$ strongly resembles the data shown in Figs. 8 and 9.

Applying the DFA analysis to the fractal signal X_η we obtain the scaling function $F_\eta(n)$ with a slope of 0.8 across all scales, in agreement with the scaling exponent $\alpha = 0.8$ we have found for healthy subjects (Fig. 10*D*). For the sinusoidal signal X_s the scaling function $F_s(n)$ exhibits a crossover at scale $n_x \approx T$, corresponding to the period of X_s. For scales $n_x < T$, the fluctuation function $F_s(n)$ exhibits an apparent scaling, $F_s(n) \sim (A/T)n^{\alpha_s}$, with an exponent $\alpha_s = 2$. For scales $n_x > T$, because of the periodic property of the sinusoidal signal X_s, the fluctuation function $F_s(n)$ is constant and independent of the scale n, i.e., $F_s(n) \sim ATn^{\alpha_s}$ where $\alpha_s = 0$. Thus changing the amplitude A leads to a vertical shift in $F_s(n)$ (Fig. 10*E* and Ref. 22).

Applying the DFA analysis to our model signal $X_{\eta s}$, we observe that $F_{\eta s}(n)$ exhibits a very pronounced kink [not present in $F_\eta(n)$] with a crossover at $n_x \approx T$ because of the sinusoidal trend (Fig. 10*F*). The behavior of $F_{\eta s}(n)$ around the kink is very similar to $F_s(n)$ around $n_x \approx T$. At small scales $n_x < T$ and at large scales $n_x > T$ the fluctuation function $F_{\eta s}(n)$ converges to the scaling behavior expected for $F_\eta(n)$. Testing our model for signals X_η with different values for α, we find that the position of the crossover n_x for $F_{\eta s}(n)$ does not depend on α. Thus this type of crossover behavior in the scaling for different subjects depends only on the period T of the periodic patterns embedded in the heart beat signals.

We find that our model in Fig. 10*F* reproduces well the crossover behavior in $F(n)$ observed for the sleep apnea subject [Apnea-ECG Database (15a) shown in Fig. 9*B*]. Indeed, a very similar kink in $F(n)$ is observed at scale $n \approx 50$ beats for this

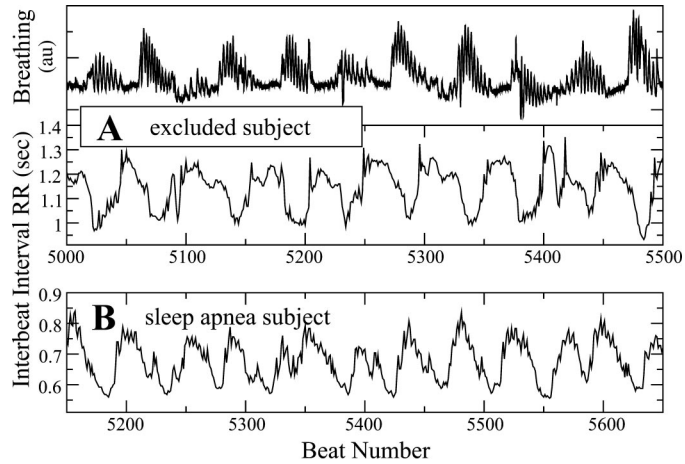

Fig. 9. Segments of interbeat R-R interval time series for (*A*) an elderly subject from the Fantasia database excluded from this study (shown in Fig. 8, *top*) and (*B*) a subject diagnosed with sleep apnea from the apnea-ECG database (see Ref. 15a). Both subjects show very similar and pronounced periodic patterns with a period of about 50 beats, matching the periodic patterns in the breathing record in *A*. These patterns strongly affect the scaling analysis as demonstrated in Figs. 10 and 11.

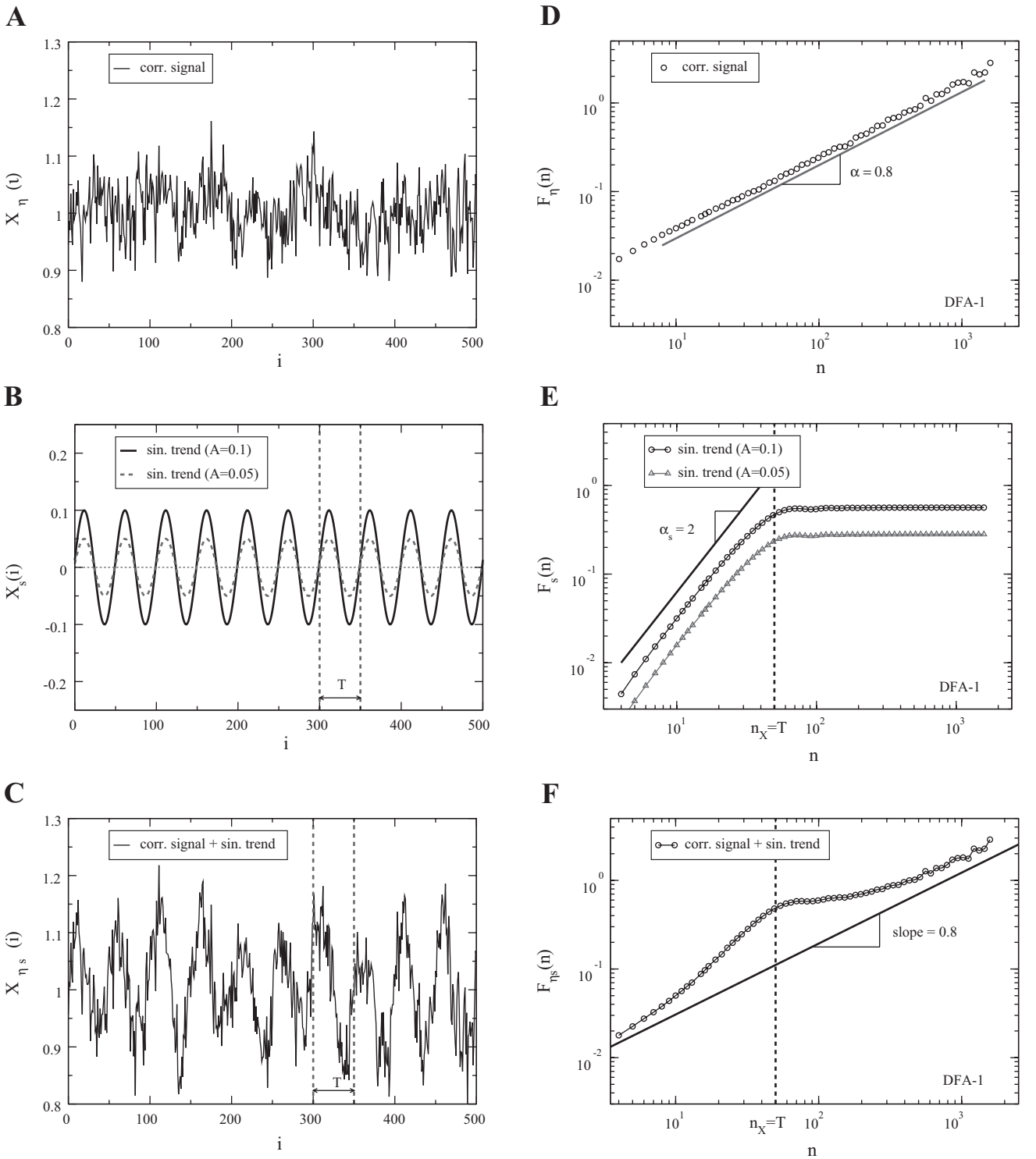

Fig. 10. Modeling crossover behavior in the scaling of heart beat dynamics associated with periodic patterns. *A*: artificially generated fractal signal X_η with long-range power-law correlations (corr), average value, and SDs as observed in healthy heart beat data. *B*: sinusoidal (sin) signal X_s with period and amplitude matching the period T and amplitude A of typical sleep apnea patterns embedded in heart beat interval time series as shown in Fig. 9. *C*: superposition of the signals X_η in *A* and X_s in *B*. Note the apparent similarity between the signal $X_{\eta s}$ and the time series shown in Fig. 9. *D*: fluctuation function $F_\eta(n)$ obtained using DFA-1 for the signal X_η in *A*. *E*: fluctuation function $F_s(n)$ obtained using DFA-1 for the signal X_s in *B*. The position of the crossover n_x corresponds to the period T in X_s. Changing the amplitude A leads to a vertical shift of $F_s(n)$. *F*: fluctuation function $F_{\eta s}(n)$ obtained using DFA-1 for the signal $X_{\eta s}$ in *C*. Note the appearance of a kink with a crossover at $n_x \approx T$ as observed in *E*.

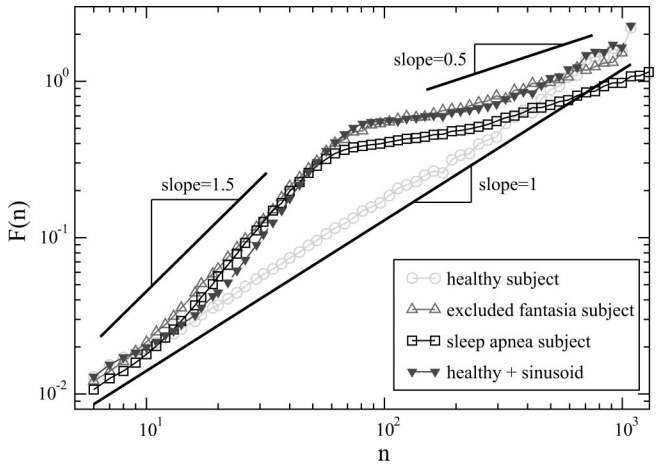

Fig. 11. Scaling functions $F(n)$ vs. time scale n obtained for the heart beat intervals using DFA-2 for a healthy subject taken from the MIT-BIH Normal Sinus Rhythm Database (15a), a Fantasia database subject we excluded from this study (15a) (shown in Fig. 9*A*), a subject with diagnosed sleep apnea (shown in Fig. 9*B*), and a healthy subject with a superposed sinusoidal signal. A period of $T = 50$ beats and an amplitude of $A = 0.1$ s were chosen for the sinusoidal signal to model the effect of periodic patterns resulting from sleep apnea on the scaling function $F(n)$. This effect leads to a change in the scaling exponent to $\alpha \approx 1.5$ (left of the crossover at T) and to $\alpha \approx 0.5$ (right of the crossover), which may be the reason why earlier studies have reported loss of fractal organization in heart beat fluctuations with healthy aging (31, 56).

apnea subject, as shown in Fig. 11. Moreover, we find that this behavior is also closely followed (as shown in Fig. 11) by the Fantasia subject in Fig. 9*A*. Adding the same sinusoidal trend to a real heart beat signal from a healthy subject [MIT-BIH Normal Sinus Rhythm Database (15a)] also leads to a very similar kink in $F(n)$ (Fig. 11).

As we demonstrate in Fig. 11, the excluded Fantasia subject shown in Fig. 9*A* exhibits a scaling curve very similar to the curve obtained from a recording during sleep from a subject diagnosed with sleep apnea [Apnea-ECG Database (15a)]. Furthermore, our model reproduces well the crossover in the scaling behavior of $F(n)$ and demonstrates that this crossover is because of the superposition of healthy heart rate dynamics and a sinusoidal trend with approximately the same period and amplitude as the periodic apnea patterns shown in Fig. 9. Our model reproduces also the scaling curve $F(n)$ obtained for the elderly Fantasia subject excluded from this study and shown in Fig. 9*A*, suggesting that artifacts may have been the reason why earlier studies (18, 31, 56) have reported scaling differences in heart beat dynamics between young and elderly subjects.

Our modeling results confirm that the presence of pronounced crossovers for some of the elderly subjects in the Fantasia database are because of periodic patterns embedded in the heart rate that strongly resemble sleep apnea episodes and, thus, cannot be attributed to changes in the underlying mechanism of cardiac neuroautonomic regulation associated with healthy aging. Because apnea is more prominent in elderly subjects, our modeling results (Figs. 10 and 11) explain why earlier studies using the same Fantasia database have reported higher values for the scaling exponent α_1 at small scales n and lower values for α_2 at large scales n for the elderly subjects compared with the group of young subjects (18, 31), claiming changes in cardiac regulation with healthy aging.

DISCUSSION

Our investigations demonstrate the presence of robust correlation, fractal, and nonlinear properties in cardiac dynamics of healthy elderly subjects that remain surprisingly stable compared with healthy young subjects. Specifically, we find that key dynamic characteristics such as the correlation scaling exponent of heart beat fluctuations, the scaling exponent of the magnitude and sign of interbeat increments, and the nonlinear fractal dimension measure do not significantly change with advanced age. Because the scaling exponents α and the fractal dimension measure D quantify a robust scale-invariant fractal and nonlinear structure in heart beat fluctuations (25, 29, 30, 53), and have been shown to reflect underlying mechanisms of cardiac control (1, 16, 27, 28), our findings indicate that important aspects of heart beat regulation do not break down with healthy aging. Moreover, we observe no significant change in these scaling and nonlinear measures when comparing healthy elderly subjects with the same subjects recorded 5 yr later.

These findings do not support the hypothesis that healthy aging may be associated with such a change in the mechanism of cardiac neuroautonomic control that would lead to a loss of all aspects of physiological complexity. In contrast, we find that fundamental scale-invariant and nonlinear properties of heart beat dynamics remain unchanged. Furthermore, our findings do not support the hypothesis of a gradual change of cardiac dynamics under healthy conditions with advanced age, since key properties of these dynamics, including heart rate variability (Table 2), remain stable in healthy elderly subjects with advancing age. Indeed, in agreement with previous studies (11, 31, 56, 65), we find a significant reduction in heart rate variability as measured by $\sigma_{R\text{-}R}$ (SDNN) and $\sigma_{\Delta R\text{-}R}$ (RMSSD) (although not in the average heart rate) in healthy elderly subjects compared with healthy young subjects (Table 2). The observed reduction in heart rate variability is also in agreement with decrease of the commonly used approximate entropy measure with aging, as reported earlier (11) and often interpreted as loss of complexity. However, comparing elderly subjects with the same subjects years later, we do not find a further reduction in interbeat variability. Moreover, we do not observe a loss in the scale-invariant fractal and nonlinear features in healthy elderly compared with healthy young subjects, indicating that the process of aging, even in elderly healthy subjects, may not result in a gradual change of the mechanism of control. Our findings support the hypothesis that *1*) only certain aspects of cardiac regulation may change with advanced age. These aspects are related to decreased responsiveness to external and internal stimuli, leading to reduced heart rate variability and *2*) other fundamental features of the neuroautonomic cardiac control may remain stable and unchanged with healthy aging. These features are related to the network of nonlinear feedback loops responsible for the neuroautonomic regulation at different time scales, leading to scale-invariant cascades in heart beat fluctuations (27, 28, 39).

This new emerging picture of healthy aging is fundamentally different from the changes in neural regulation of cardiac dynamics under pathological conditions (21, 24, 42, 43) and also differs from previous studies reporting breakdown of the scale-invariant and nonlinear features of heart beat dynamics in elderly (17, 18, 31, 41). Indeed, suppression of parasympa-

thetic tone and dominance of sympathetic inputs, typical for subjects with congestive heart failure, lead to changes in cardiac dynamics associated with higher heart rate (62, 71), lower heart rate variability (69), relative loss of the scale-invariant long-range correlations in the heart beat fluctuations with scaling exponent α between 1.25 and 1.4 (closer to $\alpha = 1.5$ corresponding to Brownian motion, i.e., random walk; see Ref. 53), reduced responsiveness (7), and breakdown of nonlinearity and multifractality (1, 25, 27, 57). In contrast to such pathological perturbations, healthy aging appears to be accompanied only by a reduction in heart rate variability as measured by $\sigma_{R\text{-}R}$ and $\sigma_{\Delta R\text{-}R}$, whereas the heart rate and the scaling and nonlinear properties remain on average unchanged. This important dissociation between heart rate variability on one side and the scale-invariant and nonlinear temporal organization of heart beat fluctuations on the other side may be specific for the process of aging and suggests that the alterations in the cardiac control mechanism with advanced age differ conceptually from the mechanistic changes in the autonomic regulation associated with pathological conditions. More specifically, the reduced heart rate variability with advanced age suggests a reduced responsiveness of cardiac control to external and internal stimuli and thus a reduced strength of feedback interactions. However, the cascade of nonlinear feedback loops (27, 28, 39) controlling the dynamics across different time scales may remain intact in healthy elderly subjects without breaking down at a particular scale or across a range of scales, since the scale-invariant fractal and nonlinear properties appear to remain stable with advanced age (Table 2). This is not the case with pathological conditions such as congestive heart failure where the self-organization of neural feedback interactions indeed breaks down across time scales, shifting the dynamics closer to a process that is more random (loss of long-range power-law correlations) and closer to a linear process (loss of nonlinearity and multifractality).

The value of the correlation exponent $\alpha_2 \approx 0.8$ we observe at intermediate and large time scales for both young and elderly Fantasia subjects (Figs. 3 and 4) is consistent with earlier reports of a very similar value of $\alpha_2 \approx 0.85$ for healthy subjects during sleep, compared with $\alpha \approx 1$ for the same subjects during wake and daily activity (29). This is also in agreement with studies of heart beat dynamics of healthy subjects during rest and exercise, with $\alpha \approx 0.8$ for rest and $\alpha \approx 1.1$ during exercise (13, 36, 48). Indeed, the Fantasia subjects were recorded under conditions of rest (see DATA AND METHODS Section I) (15a). Our findings of $\alpha \approx 0.8$ consistently for both healthy young and healthy elderly subjects from the Fantasia database are further supported by our analysis of data from the longitudinal SHHS study, where the same elderly subjects were recorded during sleep several year later. These observations of $\alpha < 1$ are not because of artifacts in the heart beat time series related to sleep apnea, since full polysomnographic data were recorded for the SHHS subjects, indicating the apnea episodes, and we have excluded the apnea segments in the data from our analysis. Moreover, our preliminary results (a focus of a subsequent study) indicate no significant differences between young and elderly subjects even when we account for rapid eye movement (REM) and non-REM (NREM) sleep stages. Because there is no statistically significant difference in the value of the scaling exponent α between the young and elderly subjects from both databases, the α value <1 is not likely to be

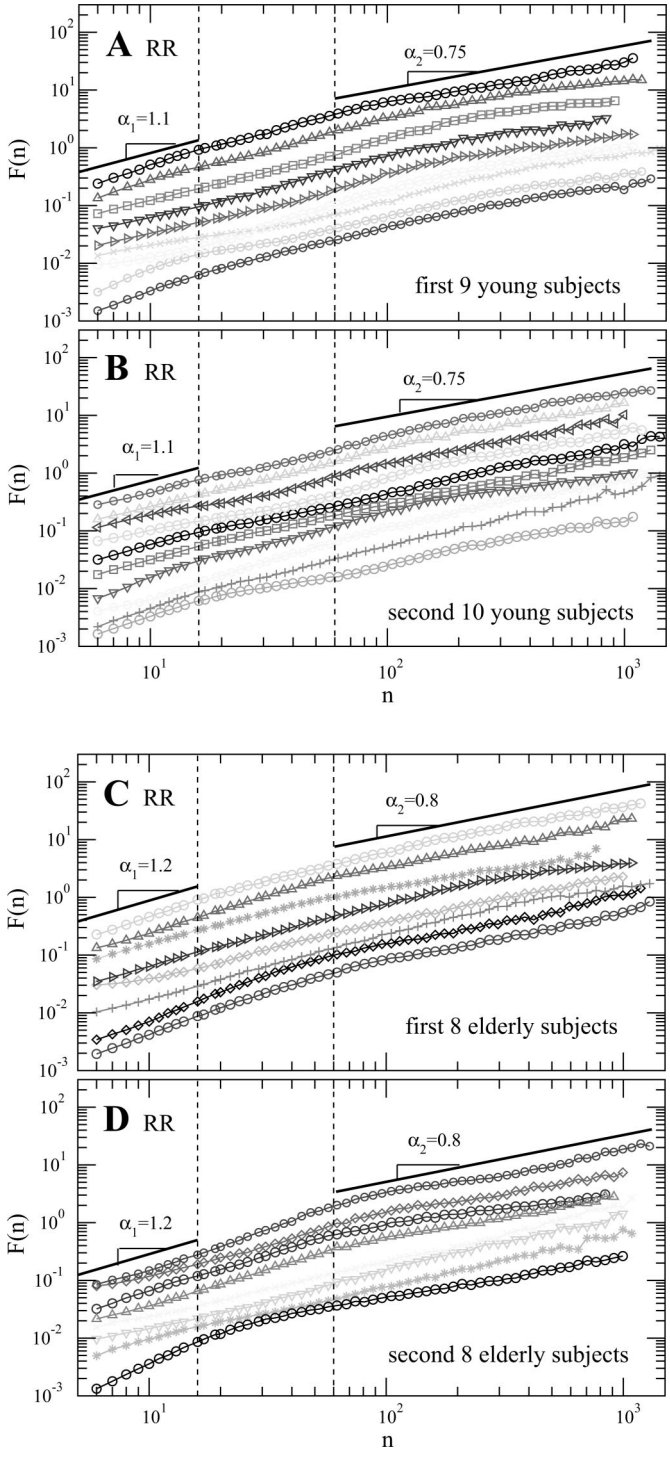

Fig. 12. Scaling curves $F(n)$ vs. time scale n (in beat numbers) obtained for the R-R heart beat intervals using DFA-2 for 19 young healthy subjects (*A* and *B*) and 16 elderly healthy subjects (*C* and *D*) in the Fantasia database. Despite certain intersubject variability, there is a very common scaling behavior with a crossover from a higher average slope α_1 at small time scales to a lower average slope α_2 at large scales as represented by the solid lines and consistent with Figs. 3 and 4. Individual curves are vertically shifted to aid visual comparison. Group average statistics are presented in Table 2. Vertical dashed lines indicate the range of fit.

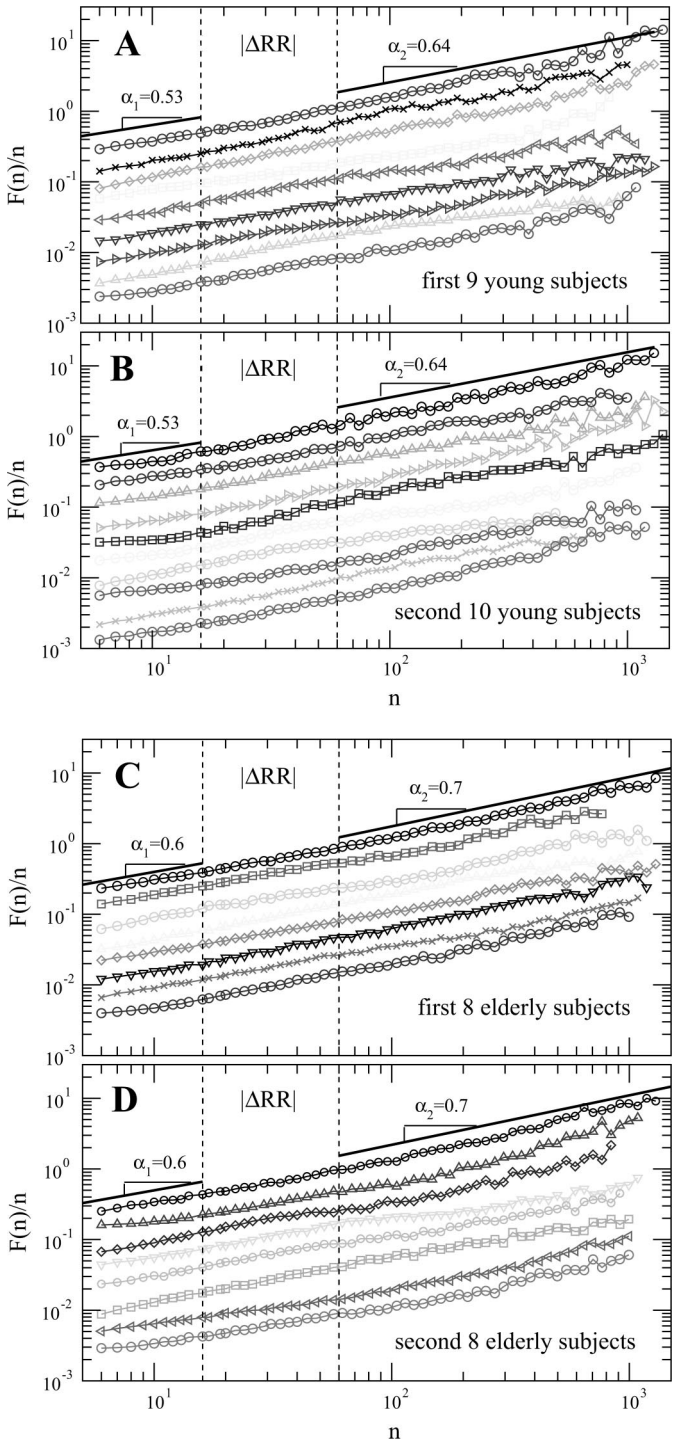

Fig. 13. Scaling curves $F(n)$ vs. time scale n (in beat numbers) obtained for the magnitude of the interbeat increments ΔR-R using DFA-2 for 19 healthy young subjects (*A* and *B*) and 16 healthy elderly subjects (*C* and *D*) in the Fantasia database. Despite certain intersubject variability, there is a common scaling behavior characterized by a group average exponent $\alpha_2 \approx 0.7$ at large scales for all groups as represented by the solid lines, indicating presence of long-term nonlinear properties encoded in the Fourier phases of the heart beat time series similar to those shown in Fig. 5. Curves are vertically shifted for clarity. Vertical dashed lines indicate the range of fit.

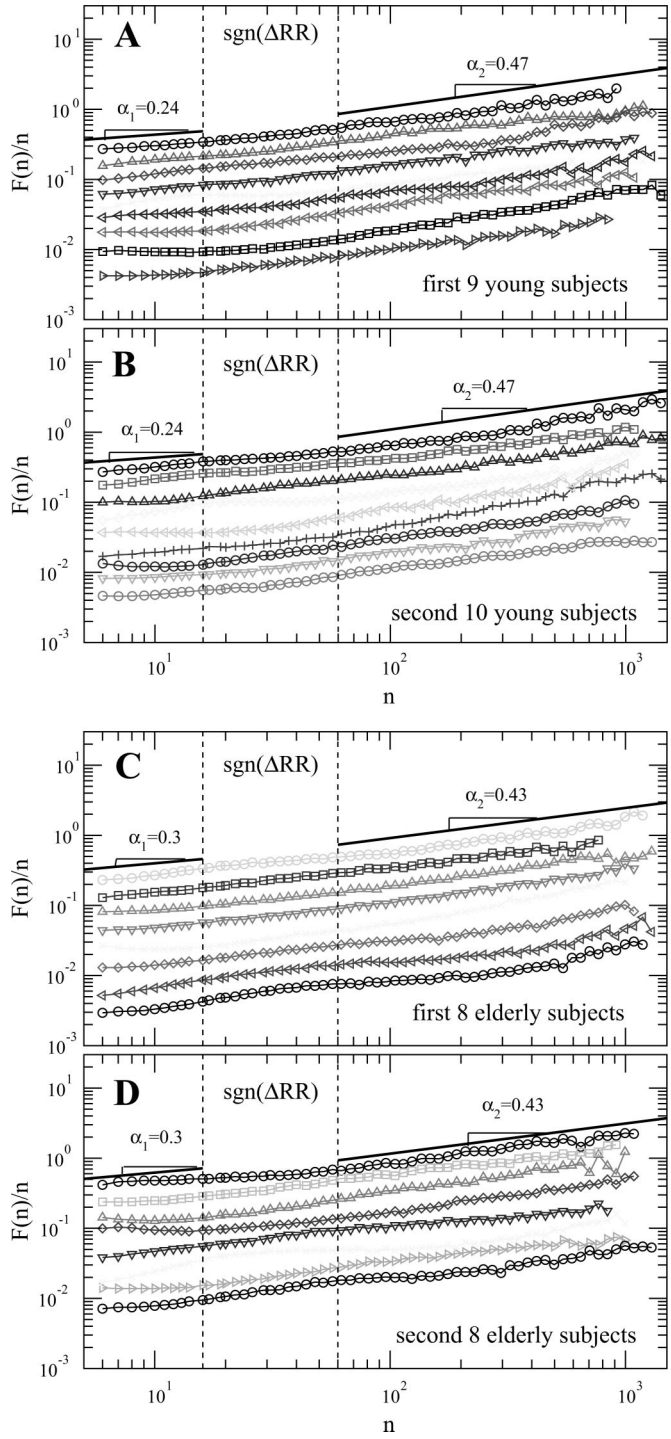

Fig. 14. Scaling curves $F(n)$ vs. time scale n (in beat numbers) obtained for the sign time series of the interbeat increments sign(ΔR-R) using DFA-2 for 19 healthy young subjects (*A* and *B*) and 16 healthy elderly subjects (*C* and *D*) in the Fantasia database. All subjects exhibit a crossover from strongly (at small scales) to weakly (at large scales) anticorrelated behavior with no significant statistical difference between the young and elderly groups (Table 2). Scaling curves are vertically shifted for clarity. Vertical dashed lines indicate the range of fit.

related to a mechanistic breakdown of cardiac control with advanced age as previously suggested (31, 56). Rather, this decrease in α is most likely to be related to the normal regime of cardiac regulation during rest and sleep when parasympa-

thetic tone dominates during NREM sleep stages, leading to stronger anticorrelations with $\alpha \approx 0.8$ in the heart beat fluctuations (8, 28, 29, 33, 36).

We find very similar results for the scaling exponent α_{mag} for the magnitude of the interbeat increments between young and elderly subjects in the Fantasia database (Table 2), as well as between the young Fantasia subjects and the elderly subjects from the SHHS database (see *P* values reported in RESULTS Section II C). These findings do not support the hypotheses that the nonlinear properties, as measured by the magnitude scaling exponent α_{mag} and encoded in the Fourier phases (64), are lost with advanced age in healthy subjects under resting conditions. We note that our results for the magnitude exponents for the young and elderly subjects from both databases are in agreement with previous studies reporting nonlinear magnitude correlations in healthy heart beat dynamics (5) and more specifically with the magnitude exponent values found in the heart rate of healthy subjects during sleep (32, 33).

Furthermore, because the dynamics of the sign (directionality) of the interbeat increments is directly related to inputs of the sympathetic and parasympathetic branches of the autonomic nervous system modulating the heart rate in opposite directions, our findings of similar scaling for the sign series for both young and elderly healthy subjects (Table 2) indicate that fundamental features of the cardiac control mechanism remain unchanged with advanced age. We also note that our results for the sign scaling exponent α^{sgn} for the young and elderly subjects from both databases are in agreement with the values reported in previous studies for healthy subjects during rest (36) and sleep (32).

Although our results do not show a significant difference in the scaling and nonlinear properties of heart beat dynamics between healthy young and healthy elderly subjects during rest and sleep, we note that, under conditions of high levels of physical activity and stress, which are associated with a different regime of the neuroautonomic control, these properties may differ between young and elderly subjects.

In summary, the observations reported here do not support the hypothesis of a continuous gradual loss of the scaling and nonlinear properties of cardiac dynamics with advanced age under healthy conditions, since we do not find a statistically significant change in these properties between the young and elderly subjects from the Fantasia and the SHHS databases as well as for the elderly subjects from the SHHS database and the same subjects recorded five years later. Although cardiac dynamics in healthy elderly subjects is characterized by markedly reduced variability compared with healthy young subjects, the stability we observe in key fractal and nonlinear characteristics with advanced age does not support the mechanistic view of a breakdown of specific feedback loops at given time scales in the neuroautonomic regulation (which would lead to appearance of dominant time scales in the dynamics) or of a breakdown of the feedback interactions in cardiac control across multiple time scales (which would lead to random-like behavior in the dynamics). Indeed, both dominant time scales and close-to-random behavior in cardiac dynamics have been observed under various pathological conditions. In contrast, cardiac dynamics under healthy aging appears not to belong to this class of processes. Instead, our results indicate that the inherent structure and temporal organization in the cascades of nonlinear feedback loops underlying the cardiac neuroautonomic regulation remain intact in healthy elderly subjects, thus preserving the fractal and nonlinear features in heart beat dynamics across all time scales. The coupling strength of these neuronal feedback interactions, however, is likely to diminish with advanced age, leading to the observed reduction in heart rate variability and dampened responsiveness in elderly compared to young healthy subjects.

APPENDIX

Results of DFA and MSA Analyses for the Heartbeat Interval Recordings for All Young and Elderly Subjects in the Fantasia Database

All subjects show a consistent behavior with: *1*) a smooth crossover from $\alpha_1 \approx 1.1$ at small time scales to $\alpha_2 \approx 0.8$ at large scales for the heart beat intervals R-R for both the young and the elderly group (Fig. 12); *2*) a smooth crossover from $\alpha_1^{mag} \approx 0.6$ at small time scales to $\alpha_2^{mag} \approx 0.7$ at large scales for the magnitude of the interbeat increments ΔR-R for both the young and the elderly group (Fig. 13); and *3*) a crossover from $\alpha_1^{sgn} \approx 0.3$ at small time scales to $\alpha_2^{sgn} \approx 0.45$ at large scales for the sign of the interbeat increments sign(ΔR-R) for both the young and the elderly group (Fig. 14).

The results show that these fractal correlation and nonlinear properties of heartbeat dynamics do not break down with healthy aging.

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