Fractal dimension of heart rate time series: an effective measure of autonomic function

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YERAGANI, VIKRAM K., K. SRINIVASAN, SATYANARAYANA VEMPATI, ROBERT POHL, AND RICHARD BALON. Fractal dimension of heart rate time series: an effective measure of autonomic function. J. Appl. Physiol. 75(6): 2429-2438, 1993.—Previous studies suggested that heart rate (HR) time series may be more appropriately analyzed by nonlinear techniques because of the nonlinear nature of these data. In this study, we quantified the complexity of the HR time series, using fractal dimension, a previously described measure developed to study axonal growth, which quantifies the space-filling propensity and convolutedness of a waveform, and compared these results with another recently used measure, approximate entropy. Fractal dimension and approximate entropy of HR time series (unfiltered) correlate highly with each other and also with the high-frequency power, LF power, and MF power and a decrease in HF power mediated by vagal withdrawal and an increase in sympathetic activity (27, 28, 32). Several previous reports used the MF/HF ratio, especially upon standing, to measure the sympathovagal interaction (27-29).

Goldberger, Lipsitz, and co-workers (10–13, 22) repeatedly stressed the importance of the nonlinear nature of HR time series and the possible advantage of using the concepts of fractals and chaos derived from the field of nonlinear dynamics to understand the function of the healthy heart. Nonlinear dynamics studies systems in which the output is not proportional to input. Mandelbrot (23, 24) dealt with “fractals” extensively in his work, and he defines fractal as irregular but with a self-similar underlying pattern. This self-similarity is obviously apparent at different levels of magnification. Fractal structures have been described in different biological systems such as bronchi, neural networks, vascular branching, and gastrointestinal folds. Examples of fractal structures abound in nature and include the trees, coastlines, mountain ranges, and clouds. Fractal structures have also been described in different biological systems (9). Recently, Kaplan et al. (17) applied one method of nonlinear techniques, approximate entropy (APEN) and approximate dimension, which are derived from the correlation integral, to time series of HR and blood pressure to study the effect of age on HR variability. APEN was derived from the Kolmogorov-Sinai entropy formula to make it a robust statistic, which is easier to compute. In a way, this statistic quantifies the regularity in time series data. This measures the logarithmic likelihood that runs of patterns that are close remain close on the next incremental comparisons and the higher the entropy value, the more random the time series (17, 30, 31).

There are several algorithms of fractal dimension (FD), including capacity dimension, information dimension, correlation dimension, and the Lyapunov dimension, and there are several different algorithms to compute FD (9). Mandelbrot (24) described this “exponent of similarity,” which he calls FD, to characterize the complexity of fractal structures. Katz and George (18–20) described a simple technique to compute FD from time series data. This specifically measures the space-filling propensity of the time series. This formula was derived from Mandelbrot’s original work in this area (23, 24). By use of this formula, the FD of a straight line is 1 and it approaches 2 for highly convoluted signals (19) (Fig. 1). This formula has been effectively used to study the growth paths of neurons (18, 20).

We have conducted several studies on HR variability in normal control subjects and patients with anxiety and depression (37–39). We found that patients with panic disorder, a form of anxiety disorder, have decreased HR variability, and they are also more sensitive to the effects of an adrenergic agent, yohimbine, which is known to produce symptoms of anxiety in these patients (5, 38). Thus important insights may be gained by studying HR variability in different frequency bands during drug challenge studies and also during pharmacological treatment.
of these disorders, inasmuch as most psychotropic agents have very strong autonomic effects.

As mentioned above, because of the nonlinear nature of HR time series, these data may be more effectively analyzed by some of the above techniques such as FD and APEN. FD and APEN may prove to be statistically effective measures of autonomic function. Especially, FD, used in this study, may not depend on assumptions such as periodicity and stationarity of the signal. These measures may have the unique advantage of being not strongly related to the means and standard deviations (SD). The main aim of this report was to apply the measure of FD by use of the computational technique described by Katz (19) to the time series of HR of three groups of subjects: normal children, normal adults, and normal adults challenged with yohimbine, which increases adrenergic activity. We were specifically interested in the relationship between age and the FD of HR after challenge with yohimbine. In this study, we compared this new measure with the measure of APEN described recently (17, 30, 31). Our results suggest that these measures are statistically very effective, FD and APEN correlate highly significantly with each other, and FD and APEN of the MF-filtered series of HR (0.05–0.15 Hz) may be used as statistically effective measures of relative sympathetic activity. To our knowledge, this is the first study to apply the above-mentioned technique to calculate FD of HR time series.

METHODS

The data for this study are from three groups of subjects: normal adults (adult group), normal children (children's group), and normal adults challenged with yohimbine (yohimbine group). Some of the data that dealt with the spectral analysis and time domain measures of the HR time series on adults and children were presented in a previous report (40). The spectral data on yohimbine were presented in another report (38). Although we use mostly the same data sets in this study, the present study is new and does not duplicate previous findings. The present study deals with the evaluation of FD, a nonlinear method of analyzing the HR time series. The techniques of FD and APEN were not available to us at the time of these initial reports. The following is a brief description of the demographic data of the above groups. The adult group consisted of 11 female and 12 male nonsmokers, 26.7 ± 4.6 yr old. The children's group consisted of five females and six males, 8 ± 2.7 yr old. The yohimbine group consisted of five females and eight males, 31.2 ± 7.2 yr old. All subjects in these groups were healthy, and routine blood tests and electrocardiograms (ECG) were within normal limits. All studies were approved by the Institutional Review Board at Lafayette Clinic (Detroit, MI). A written informed consent was obtained from each subject before their participation.

The data were collected in all the experiments after the subjects were asked to lie down quietly in the laboratory for ≥10 min after the limb leads were placed. The data were collected in supine and standing postures. Two of the adult subjects had poor recordings on the standing ECG, and thus the standing data of these subjects were excluded from the analyses. In the yohimbine experiment, data were collected in supine and standing postures before and after the yohimbine sessions in a placebo-controlled randomized design. The procedures are described in detail elsewhere (38–40).

FIG. 1. Fractal dimension (FD) of different waveforms. FD increases as convolutedness of signal increases. Note independence of this measure from mean and SD of time series.

Acquisition of the ECG Signal and Construction of the Time Series of the Data

The ECG was recorded using limb leads with a patient monitor (model 78352A, Hewlett-Packard, Palo Alto, CA) and an ECG monitor (model 78173, Hewlett-Packard). The sampling rate for the ECG signal was 500 Hz and was recorded onto a Hewlett-Packard PC by use of a 12-bit analog-to-digital converter (CIO-AD 16, Computer Boards). R-R intervals were found by taking the time difference between points of maximum derivative of successive QRS complexes. The data were replayed, and artifacts were excluded before peak detection was performed. Data with premature ventricular contractions were also excluded.

We used 256 s of real-time data in supine and standing postures for each segment of the data. From this series, instantaneous HR was obtained using the method of Berger et al. (3). The HR time series was sampled at 4 Hz so that there were 1,024 equidistant points in each of the time series. The power spectrum was obtained as the magnitude squared of the fast Fourier transform by use of a rectangular data window. The power spectra were integrated over MF (0.07–0.15 Hz) and HF (0.2–0.6 Hz) bands. However, we also included the power in the 0.15–0.5-Hz band to ensure that this did not change any of
correlate well with the HF power time series. This measure has been previously found to the successive squared differences of the consecutive HR

these analyses using the MF and HF powers obtained from spectral analysis, only to correlate with the corresponding measures of FD. We obtained the mean, variance, and the root mean successive square difference (rMSSD) from the instantaneous unfiltered (UF) HR time series. The rMSSD is the square root of the mean of the successive squared differences of the consecutive HR time series. This measure has been previously found to correlate well with the HF power (0.2–0.5 Hz) of the HR time series, which is related to the vagal modulation of HR variability (4, 36).

**Digital Filtering of the Data**

The data were digitally filtered to obtain a series of the data predominantly reflecting the Mayer wave frequency (0.05–0.15 Hz) and another series reflecting predominantly the respiratory frequencies (>0.15 Hz). Each data segment was digitally filtered using band-pass and high-pass filters to obtain a series with a pass band of 0.05–0.15 Hz and another series with a pass band >0.15 Hz. For the band-pass filter we used a transition bandwidth of 0.025 Hz, and for the high-pass filter we used a transition bandwidth of 0.0176 Hz. Figure 2 illustrates the frequency response of the filters used. We eliminated the first 50 and the last 50 data points of the filtered data for the MF series and the first 16 and the last 16 data points for the high-pass filter because of the nature of the filtering algorithms (6). Thus each supine and standing segment of the data has UF, MF (0.05–0.15 Hz), and HF (>0.15 Hz) segments (Fig. 3). FD and APEN were obtained for all these series of data for the three groups of subjects by use of the following techniques.

**FD**. The following is a brief description of the FD method as stated by Katz and George (20)

\[ D = \log \left( \frac{L}{a} \right)/\log \left( [K/a]A \right) \]  

where \( D \) is the fractal dimension, \( L \) is the total length of the curve, \( a \) is the average step length \( (a = L/n, \text{where} n \text{is the total number of steps}) \), \( K = 2/\pi \), and \( A \) is the area of the circle potentially filled by an ideal random walk.

From Eq. 1, they obtained the following after removing the constant \( K \) from the formula

\[ D = \log \left( \frac{n}{\log (nd/L)} \right) = \log \left( \frac{n}{[\log (n) + \log (d/L)]} \right) \]

where \( L \) is the sum of distances between successive points, \( d \) is the planar extent of the curve, which is the farthest distance between starting point and the “ith” point of the time series, and \( n \) is the number of steps in the curve.

The FD of a planar curve is defined as follows

\[ FD = \log \left( \frac{L}{d} \right)/\log \left( d \right) \]

\[ FD = \log \left( \frac{L}{d} \right)/\log \left( A \right) \]

where \( L \) is the total length of the curve and \( d \) is the diameter (planar extent) of the curve. As suggested by Katz (19), we adopted the formula

\[ FD = \log \left( \frac{L}{a} \right)/\log \left( d/a \right) = \log \left( \frac{n}{[\log (n) + \log (d/L)]} \right) \]

where \( n \) is the total number of steps in the curve (total number of points - 1) and \( a \) is the average distance between successive points. Using a customized software program, we followed the method of computation suggested by Katz (19).

**Conservative FD**. The only difference in this computation is the calculation of \( d \), which is measured as the distance between the minimum and maximum values of the time series signal on the y-axis. However, the underlying assumption is that one of these values occurred at the starting point and the other at the end point. This will ensure that \( d \) is calculated from the maximum distance between any two points of the time series signal.

**APEN**. Two input parameters must be set before the analysis: the run length \( (m) \) and the filter level \( (r) \). From previous reports, a value of 2 for \( m \) and a value of 0.2 times the SD of the time series for \( r \) appear to give useful values of APEN. We followed the original method suggested by Pincus et al. (30, 31) to compute the APEN.

APEN is derived from the correlation integral \( C_m(r) \), which is the number of points in the signal closer than
distance \( r \) to the \( i \)th point when embedded in an \( m \)-dimensional space.

Here APEN is defined as

\[
\text{APEN}(m, r) = \Phi^m(r) - \Phi^{m+1}(r)
\]

where

\[
\Phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln \frac{C^m(r)}{N \cdot m \cdot (m-1)}
\]

Pincus, Kaplan, and co-workers (17, 31) suggested that when \( m = 2 \) and \( r = 0.2 \) times the SD of the time series, one obtains reasonable values of APEN. Inasmuch as our calculated \( r \) value was \(-1\) for most of the subjects, we used a filter level of 1 in this study. Inasmuch as our time series is only 256 s, we wanted to use \( \approx 1,000 \) data points and we wanted to correlate FD and APEN values with the spectral measures (MF and HF powers), we used the time series sampled at 4 Hz, which has 1,024 data points. This resulted in lower values of APEN in our study than in the study of Kaplan et al. (17), where they used a lag of approximately one beat (800 ms). When we used our data sampled at 1 Hz, our APEN values were very similar to those in the above-mentioned study. We have also noticed that increasing the sampling rate of the time series (decreasing the distance between 2 successive time points) has resulted in a predictable decrease in APEN values. All these calculations were performed on a PC with a customized software program according to the method of Pincus et al. (31).

**Statistical Analysis**

We used BMDP statistical software (Berkeley, CA) to perform the analyses. The main outcome measures of this study were FD and APEN.

We used a three-way analysis of variance (ANOVA) with two repeated measures to compare the UF, MF, and HF measures in supine and standing conditions between children and adults. Significant main and interaction effects were followed up with two-tailed \( t \) tests with Bonferroni correction for multiple tests. For the yohimbine data, we analyzed only the MF data before and after the administration of yohimbine by means of two-tailed \( t \) tests. The main purpose of these comparisons was to determine the robustness of the measures FD and APEN compared with pre- and postyohimbine MF powers in the standing posture in our previous report (\( P = 0.04 \)) (38).

We also performed linear regressions using age as the dependent variable and the measures of FD, APEN, and variance of the time series as the independent variables. We calculated the standard error of \( y \) estimate (SEE) for the linear regressions using the following formula. This measure indicates the goodness of fit for the linear regressions along with the correlation coefficients (7)

\[
\text{SEE} = \sqrt{\frac{\sum (y_i - \hat{y}_i)^2}{N - p}}
\]

where \( y_i \) is the observed value of \( y \) at the \( i \)th point, \( \hat{y}_i \) is the predicted value of \( y \) at the \( i \)th point, \( N \) is the sample size, and \( p \) is the number of independent variables.

Katz and George (19, 20) recommended the use of log transformation of FD data, inasmuch as the data in their studies on neuronal growth were lognormally distributed. In this study, the distributions were very similar between the raw FD values and the log FD values, and there was very little difference between the results of parametric and nonparametric statistical analysis of FD or log FD. Hence we elected to present the parametric test results on the raw FD values.

We also used the variance of the MF- and HF-filtered time series to compare with the corresponding FDs to determine whether filtering itself made the comparisons between children and adults more robust.

**RESULTS**

Figure 3 shows the FD and the APEN values for UF, MF, and HF series of HR data of a normal subject in supine and standing postures.
Children and Adults

Three-way ANOVA for the comparison of the FD values of children and adults showed a significant difference between the groups \(F = 32.8, df = 1, 30, P = 0.00001\), a significant posture effect \(F = 18.7, df = 1, 30, P = 0.00002\), a frequency effect \(F = 519.0, df = 2, 60, P = 0.00001\), and a posture vs. frequency effect \(F = 93.9, df = 2, 60, P = 0.00001\); Fig. 4). These results illustrate that children had significantly higher values of UF, MF, and HF FD than adults and that the UF and HF values were significantly higher than the MF values (Fig. 4). This was also true for the analyses of APEN values \(F = 32.6, df = 1, 30, P = 0.00001\); posture effect: \(F = 17.8, df = 1, 30, P = 0.00002\); frequency effect: \(F = 498.5, df = 2, 60, P = 0.00001\); Fig. 4). Figures 3 and 4 also illustrate that whereas there was a significant decrease of UF and HF values of FD and APEN during the standing posture, there was a significant increase of MF values during the standing posture for the adults.

The ratios of sympatovagal balance, as calculated by MF/HF ratios, were significantly higher in adults than in children in supine and standing postures for the FD values \(F = 32.8, df = 1, 30, P = 0.00001\); supine: \(t = 6.2, df = 30, P = 0.00001\); standing: \(t = 6.2, df = 30, P = 0.00001\). These were less robust for the corresponding APEN values \(t = 1.5, df = 32, P = 0.15\); supine: \(t = 6.2, df = 30, P = 0.00001\). Children had lower MF/HF ratios (spectral) in supine and standing postures \(P < 0.005\); Fig. 4).

Table 1 illustrates the relationship between age and the supine and standing FD and APEN measures. There were highly significant relationships between age and UF and HF measures for FD and APEN values \(r = 0.99\); Fig. 5). Correlations of age and MF/HF ratios were significant only for the FD measures and standing APEN (Table 1, Fig. 6).

There were highly significant correlations between the UF FD and the corresponding APEN measures (supine: \(r = 0.99\), standing: \(r = 0.99\); Fig. 7). The FD values of the MF series correlated highly with the corresponding MF power in supine and standing postures \(r = 0.96\) and 0.95, respectively). The FD values of the HF series also correlated highly with the corresponding HF power in supine and standing postures \(r = 0.94\).

FD values of the UF time series in supine and standing postures correlated highly significantly with the corresponding rMSSDs of the UF time series \(r = 0.98\) and with the HF power (spectral) \(r = 0.89-0.94\) compared

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine</th>
<th>Standing</th>
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<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>SE</td>
</tr>
<tr>
<td>Variance</td>
<td>-0.61†</td>
<td>7.81</td>
</tr>
<tr>
<td>MF power</td>
<td>-0.51†</td>
<td>8.53</td>
</tr>
<tr>
<td>MF variance</td>
<td>-0.51†</td>
<td>8.49</td>
</tr>
<tr>
<td>HF power</td>
<td>-0.62*</td>
<td>7.79</td>
</tr>
<tr>
<td>HF variance</td>
<td>-0.62*</td>
<td>7.79</td>
</tr>
<tr>
<td>rMSSD</td>
<td>-0.69*</td>
<td>7.20</td>
</tr>
<tr>
<td>FD</td>
<td></td>
<td></td>
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<tr>
<td>UF</td>
<td>0.76*</td>
<td>6.30</td>
</tr>
<tr>
<td>MF</td>
<td>-0.41†</td>
<td>9.01</td>
</tr>
<tr>
<td>HF</td>
<td>-0.76*</td>
<td>6.41</td>
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<tr>
<td>MF/HF</td>
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<td>6.44</td>
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<tr>
<td>APEN</td>
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<tr>
<td>UF</td>
<td>-0.79*</td>
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</tr>
<tr>
<td>MF</td>
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</tr>
<tr>
<td>HF</td>
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<td>6.16</td>
</tr>
<tr>
<td>MF/HF</td>
<td>0.14</td>
<td>9.78</td>
</tr>
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</table>

UF, unfiltered; MF, midfrequency; HF, high frequency; SE, standard error of \(y\) (age) estimate; FD, fractal dimension; APEN, approximate entropy; rMSSD, root successive square difference. * \(P < 0.0001\); † \(P < 0.005\); ‡ \(P < 0.02\).
FIG. 5. Linear regressions of age with UF FD, UF APEN, and variance of heart rate in supine and standing postures. Note better fit with FD and APEN.

with the correlations with the corresponding variances (supine: \( r = 0.86 \); standing: \( r = 0.64 \)) and the means (supine: \( r = 0.35 \); standing: \( r = 0.23 \)) of the time series (Fig. 7).

**Yohimbine Group**

The postyohimbine standing MF FD and MF APEN were significantly higher than the preyohimbine values

(t = 3.7, df = 11, P = 0.004 and t = 2.72, df = 11, P = 0.02, respectively; Fig. 8). The comparison using the MF variance was less robust (t = 1.33, df = 11, P = 0.08). Log conversion of the values of the MF variance improved the probability only to 0.04. There was also a high degree of correlation between MF FD and MF APEN measures for pre- and postyohimbine conditions \((r = 0.99)\). In our previous study (38), when we compared the pre- and postyohimbine MF power from the spectral data, the difference was statistically less significant \((23.0 \pm 17.7 \text{ vs. } 31.3 \pm 28.3 \text{ beats/min}^2; t = 2.4, df = 11, P = 0.04)\).

**FD and Conservative FD**

These measures were almost identical. However, the conservative FD was always slightly lower than the original value, as expected. All the results of the above analyses were almost identical by use of either measure.

Analyses Using HF Power Between 0.15 and 0.5 Hz

The results of these analyses were very similar to the results obtained using the 0.2- to 0.5-Hz band. The correlation coefficients between age and the supine and standing HF power were \(-0.53\) and \(-0.54\), respectively, and those between age and MF/HF ratios were \(0.36\) and \(0.29\) for the supine and standing conditions. The difference in the MF/HF ratios between children and adults was significant for supine \((t = 2.15, df = 32, P = 0.04)\) and less pronounced for standing \((t = 1.98, df = 30, P = 0.06)\) conditions.
**Analyses Using Variance of the MF and HF Filtered Time Series**

The results of these analyses were similar to those obtained by the analyses using the spectral MF and HF powers of the unfiltered time series (Table 1). The correlation coefficients between age and the supine and standing MF/HF ratios were 0.39 and 0.44, respectively. The difference in the MF/HF ratios between children and adults was significant for supine ($t = 2.37$, df = 32, $P = 0.024$) and standing ($t = 3.18$, df = 30, $P = 0.003$) positions.

**DISCUSSION**

This study suggests that FD and APEN can be used to study the complexity and the irregularity of the time series of HR in humans. There is a very high degree of correlation between the FD and the corresponding APEN values. The fact that FD and APEN of the UF time series decrease from the supine to the standing posture and correlate very highly with the HF power and also rMSSD suggests that these measures reflect modulation of vagal activity, inasmuch as there is a decreased vagal activity during the standing posture. This is further supported by a significant negative correlation between age and UF FD and UF APEN, because aging is associated with a decrease in vagal modulation of HR (22, 35, 40). The correlation between age and UF FD and UF APEN is higher than the correlation of age with the supine and standing variances or the HF power on spectral measures in our previous study (40). In our previous report, these correlation coefficients were 0.31–0.62 compared with 0.60–0.79 in this study. Thus FD and APEN appear to be statistically more effective.

In this study, we also obtained the FD and APEN for the filtered time series to study the MF and HF time series. The results are consistent with previous reports on spectral measures with regard to postural changes. There was a significant increase of FD1 and APEN of the MF series during the standing posture in adults and a significant decrease of the values of the HF series in the standing posture compared with the supine posture in adults and children. For the comparisons between children and adults, FD of the UF series was significant at $P = 0.00001$ ($t = 5.8$) compared with the variance ($t = 3.6$, $P = 0.001$). As can be seen from Fig. 5, for the supine UF FD, 6 adults had higher values of FD than the lowest value for the children's group, whereas for the supine variance, 16 adults had higher values than the lowest value for the children's group. It should also be noted that whereas the mean supine UF FD for the children's group is 2 SDs above the corresponding mean for the adult group, the supine variance of the UF time series for the children's group is only 1 SD above the corresponding mean for the adult group.

Several previous studies used the MF/HF power ratios to study the sympathovagal interaction (27–29). In the present study, these ratios of FD correlated positively with age, and supine and standing ratios were significantly higher in adults than in children ($P = 0.00001$), which suggest that aging produces an increase in relative sympathetic modulation of HR variability in the age range studied. Also the differences of supine and standing MF/HF ratios (spectral) between children and adults were less robust in our previous report using spectral measures ($P = 0.005$; Fig. 4) (40). For the MF/HF ratios, the FD measures were most effective for the comparison of adults and children. This was true even when we compared the analyses using variance of the MF and HF filtered time series and their ratios to the corresponding analyses using FDs. The results of the analyses using the 0.15- to 0.5-Hz band for the HF power also did not change any of the results significantly compared with the analyses using the 0.2- to 0.5-Hz band.

In our previous study on the effects of yohimbine, we found that yohimbine produced an increase in standing MF power in normal controls ($P = 0.04$), which suggested that the adrenergic effects of yohimbine may play a role in this regard (38). Yohimbine also produced significant increases in systolic and diastolic blood pressure in supine and standing postures. As shown in Fig. 8, the FD of the MF series was more robust for the comparison of the pre- and postyohimbine conditions than the variance of the filtered MF time series, which also suggests that FD of the filtered time series may be effectively used to study the relative sympathetic influences on HR variability. Although digital filtering does not eliminate the unwanted frequencies completely, the results of this study were much more robust than the corresponding spectral measures. The measure of FD appears much more sensitive and thus may prove useful in comparing different populations.

FD and APEN of the UF time series correlated well with the rMSSD but less significantly with the variance of the time series and poorly with the mean values. This again suggests that these measures are relatively independent of mean and variance of the time series. In this study, FD measures correlated better with age in general and also distinguished between children and adults more effectively than the spectral measures and variance. This was especially true with the MF/HF ratios, which have been used to indicate sympathovagal interaction of HR variability (27–29).

Unlike spectral analysis, FD may be used on the time series (UF) even when the assumption of periodicity is not met. This is especially important for the analysis of biologic variables such as HR and blood pressure time series. Inasmuch as the FD measures are statistically more effective, FD may be able to detect relatively smaller differences between two sets of time series when the conventional measures of SD and power spectral measures are unable to detect such differences. We should also point out that even analyses using log conversion of variance or spectral measures were less significant than the analyses using FD. The most likely reason for this is the smaller variance of FD around the mean for each group. In this study, whereas the standing variance of the HR time series was not significantly different between children and adults, the FD values were significantly higher in children ($P = 0.0004$), suggesting that, with increasing age, there is a decrease in the complexity of the HR time series. In fact, this is in agreement with
the findings of Kaplan et al. (17), who also found that the older subjects had a significantly lower APEN of systolic blood pressure despite a higher variance. Thus the measures of FD appear to be useful additions to study autonomic function in physiological, pharmacological, and other clinical studies.

The waveforms of time series such as HR are planar curves that go forward and do not cross over. Because of the nonlinear nature of these curves, spectral techniques such as Fourier analysis may not be ideal, because it approximates waveforms as a series of cosine and sine waves. In contrast to these analyses, FD of a pattern is a measure of its complexity and its spatial extent and is dependent of the dimensionality and the shape of the pattern (19). Fractal characterization can be applied to various sets of data such as evolutionary data (19) and characterization of blood flow, which is a means of describing the contribution of sample piece size to the calculated heterogeneity of flow (9). Fractal structure has also been described in biologic structures including pulmonary bronchial and vascular trees (8, 14), boundary lengths of alveoli (33), vasculature of the myocardium (2), and time series of HR (11). Thus it may be more appropriate to understand the behavior of these systems by use of nonlinear techniques such as FD and APEN than the traditional methods of data analysis. Glenny et al. (9) argue that a coding for self-similar structures is the most efficient appropriate algorithm to explain the order and the complexity of ontogeny. In this context, loss of complexity or becoming increasingly regular, as is the case for the HR time series, can be construed as a sign of abnormality, which has been extensively dealt with previously (11).

Finally, it appears that the measures of FD and APEN can be used interchangeably, inasmuch as there is a very high degree of correlation between these measures. However, from the standpoint of nonmathematicians, the measure of FD may be much simpler to understand and to use than the highly technical and sophisticated measure of APEN. For APEN, the investigator also has to fix the filter level may change with the SD, this may pose difficulties when populations with significantly different SDS are to be compared. Although there was such a high degree of correlation between FD and APEN values, one should note that this will not always be true, especially when one deals with a periodic signal. In this instance, APEN will be 0 but FD will not be 1. In this study, FD was a statistically more effective measure, especially to evaluate the effect of age on MP/HP ratios.

There was very little difference between FD and the conservative FD, which suggests that for time series such as HR the farthest point from the starting point can be used to calculate the value of $d$.

Inasmuch as there were very few studies of HR variability using nonlinear techniques and because the technique presented in this study has not been used before to calculate the FD of the HR time series, we caution readers that such new techniques should be used in conjunction with widely accepted techniques such as the traditional time and frequency domain measures of HR variability until further studies demonstrate the utility of these new measures, especially in acute pharmacological intervention studies.

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