Cardiac Interbeat Interval Dynamics From Childhood to Senescence

Comparison of Conventional and New Measures Based on Fractals and Chaos Theory

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Background—New methods of R-R interval variability based on fractal scaling and nonlinear dynamics (“chaos theory”) may give new insights into heart rate dynamics. The aims of this study were to (1) systematically characterize and quantify the effects of aging from early childhood to advanced age on 24-hour heart rate dynamics in healthy subjects; (2) compare age-related changes in conventional time- and frequency-domain measures with changes in newly derived measures based on fractal scaling and complexity (chaos) theory; and (3) further test the hypothesis that there is loss of complexity and altered fractal scaling of heart rate dynamics with advanced age.

Methods and Results—The relationship between age and cardiac interbeat (R-R) interval dynamics from childhood to senescence was studied in 114 healthy subjects (age range, 1 to 82 years) by measurement of the slope, $\beta$, of the power-law regression line (log power–log frequency) of R-R interval variability ($10^{-3}$ to $10^{-2}$ Hz), approximate entropy (ApEn), short-term ($\alpha_1$) and intermediate-term ($\alpha_2$) fractal scaling exponents obtained by detrended fluctuation analysis, and traditional time- and frequency-domain measures from 24-hour ECG recordings. Compared with young adults (<40 years old, n=29), children (<15 years old, n=27) showed similar complexity (ApEn) and fractal correlation properties ($\alpha_1$, $\alpha_2$, $\beta$) of R-R interval dynamics despite lower overall heart rate variability. Progressive loss of complexity (decreased ApEn, $r=-0.69$, $P<0.001$) and alterations of long-term fractal-like heart rate behavior (increased $\alpha_2$, $r=0.63$, decreased $\beta$, $r=-0.60$, $P<0.001$ for both) were observed thereafter from middle age (40 to 60 years, n=29) to old age (>60 years, n=29).

Conclusions—Cardiac interbeat interval dynamics change markedly from childhood to old age in healthy subjects. Children show complexity and fractal correlation properties of R-R interval time series comparable to those of young adults, despite lower overall heart rate variability. Healthy aging is associated with R-R interval dynamics showing higher regularity and altered fractal scaling consistent with a loss of complex variability. (Circulation. 1999;100:393-399.)

Key Words: aging ■ heart rate ■ fractals

Cardiac interbeat interval dynamics vary with age in healthy subjects, possibly in relation to changes in the regulatory mechanisms. The maturation of the autonomic nervous system and other control systems during childhood is associated with increased variation of heart rate (HR).1,2 Conversely, increasing age during adult life is associated with a reduction in overall HR variability2-7 and also in the complexity of physiological dynamics.8,9 This loss of complexity may be due to both structural factors (eg, loss of sinoatrial pacemaker cells) and functional changes (eg, altered coupling between these components).9 The loss of complexity and alterations of long-range (fractal) organization with aging, which are also apparent in many diseases,10 may be associated with the reduced ability to adapt to physiological stress.

Recently, new dynamic methods of R-R interval variability have been used in conjunction with traditional time- and frequency-domain measures to uncover “hidden” abnormalities and alterations that are not otherwise apparent.9 A number of studies have addressed the effects of age on R-R
interval dynamics. Reduced HR variability and loss of HR complexity have been reported with increasing age.\textsuperscript{2–8,11,12} However, previous studies have important limitations related to analyses based solely on traditional time- and frequency-domain measures.\textsuperscript{2–5,7} on short-term (<3 hours) ECG recordings,\textsuperscript{6,11,12} or on comparisons between small groups with widely disparate ages but without including children.\textsuperscript{8,11}

The purpose of the present study, therefore, was to systematically investigate the effects of age on R-R interval dynamics from 24-hour ECG recordings in healthy subjects over a wide range of ages (childhood to advanced age). In addition to traditional measures of HR variability, we used recently described methods derived from nonlinear dynamics (chaos theory) and fractal analysis, including scaling exponents derived from the power spectrum\textsuperscript{13–15} and detrended fluctuation analysis (DFA).\textsuperscript{11,16} and approximate entropy (ApEn).\textsuperscript{17–19} a “complexity” measure.

\section*{Methods}

\subsection*{Subjects}

One hundred fourteen healthy subjects (age range, 1 to 82 years) were included in this cross-sectional study. The subjects were divided into 4 groups: (1) children, <15 years old (mean, 8.5 ± 5 years); (2) young adults, 15 to 40 years old (mean, 28.6 ± 6 years); (3) middle-aged, 40 to 60 years old (mean, 50 ± 6 years); and (4) elderly, >60 years old (mean, 71 ± 5 years). There were 15 boys and 12 girls in the group of children and 17 men and 12 women in each other group. The children and young adults were apparently healthy, with no history or symptoms of heart disease, hypertension, or diabetes, and with normal findings on clinical examination. The middle-aged\textsuperscript{20} and elderly subjects\textsuperscript{21} were selected from previously described random populations. All middle-aged and elderly subjects underwent a physical examination, a standard 12-lead ECG, a chest radiograph, and laboratory tests. No subjects with a previous history, symptoms, or clinical evidence (including analysis of ECG data, including \textit{a}的心律失常, \textit{b}的电生理学特征, and \textit{c}的临床表现) of ischemic heart disease, diabetes, hypertension, or any other medical disorder were included. The fasting blood glucose was <6.7 mmol/L and the blood pressure <160/90 mm Hg in all subjects. None of the subjects included were taking any medication. All subjects gave informed consent. The study protocol was approved by the Ethics Committee of the University of Oulu.

\subsection*{HR Recordings}

A 24-hour ambulatory ECG recording was performed during usual everyday activities. All subjects had \(\geq 18\) hours (mean, 23 ± 1 hours) of ECG data, including \(\geq 90\%\) of normal sinus beats. The ECG data were digitally sampled (frequency, 256 Hz) and transferred from a scanner to a microcomputer for the analysis of HR variability. Premature beats and artifact were carefully eliminated automatically and manually.\textsuperscript{22} The measures of R-R interval dynamics were calculated from the entire 24-hour recording and also separately for the hours representing nighttime (midnight to 6 AM) and daytime (9 AM to 6 PM) hours to study possible diurnal differences.

\subsection*{HR Variability Measures}

\textbf{Time- and Frequency-Domain Measures}

The mean and the SD of all R-R intervals (SDNN) were used as time-domain measures of HR variability. The power spectrum densities were estimated by the fast Fourier method. Ultralow-frequency power (ULF, <0.0033 Hz) and very-low-frequency power (VLF, 0.0033 to 0.04 Hz) were calculated from the entire 24-hour segment. Low-frequency power (LF, 0.04 to 0.15 Hz), high-frequency power (HF, 0.15 to 0.4 Hz), and the nighttime and daytime VLF powers were calculated from 1-hour segments of the 24-hour recording. The mean value of these segments was used.

\textbf{Fractal Scaling and Complexity Measures: Power-Law Relationship Analysis}

The slope, \(\beta\), of the power spectrum was calculated as described previously\textsuperscript{13–15} by a regression analysis of log(power) and log(frequency) plots of the smoothed power spectrum over the frequency range of \(10^{-4}\) to \(10^{-2}\) Hz. This range was chosen because of the typically linear (\(1/f^{\beta}\)) relationship between log(power) and log(frequency) over this broad frequency band.\textsuperscript{13}

DFA quantifies fractal-like correlation properties of the time-series data.\textsuperscript{11,16} The root-mean-square fluctuation of the integrated and detrended data are measured in observation windows of various sizes and then plotted against the size of the window on a log-log scale. The scaling exponent \(\alpha\) represents the slope of this line, which relates (log)fluctuation to (log)window size. In this study, both \(\alpha_s\), the short-term (4 to 11 beats) and \(\alpha_t\), the intermediate-term (>11 beats) scaling exponents were calculated. The scaling exponents were calculated from segments encompassing 8000 beats of the 24-hour ECG recording as previously described.\textsuperscript{11,16} and the average values of these segments were used.

Approximate entropy, a measure quantifying the regularity of time series, was calculated from the average values of segments encompassing 8000 beats with fixed input variables \(m=2\) and \(r=20\%\) as previously described.\textsuperscript{17–19} In addition, \(\alpha_s\), \(\alpha_t\), and ApEn were calculated from segments encompassing 4000 beats from 3-hour periods (midnight to 3 AM, 3 to 6 AM, 9 to 12 AM, noon to 3 PM, 3 to 6 PM) to obtain nighttime (midnight to 6 AM), early sleeping phase (midnight to 3 AM), and daytime (9 AM to 6 PM) average values.

\textbf{Statistics}

Results are reported as mean ± SD. The data were normally distributed. However, the distributions of the spectral values of HR variability were highly skewed. Therefore, these data were transformed by taking the natural logarithms of the absolute values. Parametric tests were used to compare the groups and to test the correlations among age and measures of HR dynamics based on the results of the Kolmogorov-Smirnov test (\(z<1.0\)) for a normal distribution. The comparisons between the 4 study groups were analyzed by 1-way ANOVA followed by the Bonferroni post hoc test. Student’s \(t\) test was used to compare males and females and nighttime and daytime values. Pearson’s correlation coefficients (\(r\)) are given when linear relationships between 2 variables are reported. A value of \(P<0.05\) was considered statistically significant.

\textbf{Results}

Representative examples of R-R interval time-series, 24-hour power-spectra, power-law, and scaling DFDAs of data from a 7-year-old, a 29-year-old, and a 76-year-old healthy male are shown in Figures 1 and 2. Different measures of HR dynamics as a function of age are plotted in Figures 3 to 5.

\textbf{Children Versus Young Adults}

Measures of complexity (ApEn) and short-term \(\alpha_t\) and longer-term temporal correlation properties \(\alpha_s\) and \(\beta\) of R-R intervals did not differ between children and young adults.
However, the total variance and all the power spectral measures were lower in children than in young adults. A linear increase in all time- and frequency-domain measures was observed during childhood ($r$ between 0.66 [HF] and 0.78 [VLF], $P<0.001$ for all), and children $<6$ years old ($n=10$) had significantly lower values than children between 6 and 15 years old ($n=17$) ($P<0.01$ for all). No differences were found in ApEn, $\alpha_1$, and $\beta$ between children in the 2 age groups. Children 6 to 15 years old had significantly lower total variance than young adults, but their dynamic measures did not differ.

Comparisons of HR variability measures during daytime (9 AM to 6 PM) and nighttime (midnight to 6 AM) did not reveal differences in ApEn or scaling exponents between the children and young adults. Furthermore, when measures of HR variability were compared between the groups during the early phase of sleeping hours (midnight to 3 AM), no differences between the age groups were observed in ApEn (1.39±0.13 in children versus 1.36±0.19 in young adults, $P=NS$), $\alpha_1$ (0.88±0.19 versus 1.00±0.21, $P=NS$), or $\alpha_2$ (0.92±0.11 versus 0.95±0.10, $P=NS$), despite the lower overall variance in children (SDNN 95±43 ms in children versus 133±40 ms in young adults, $P<0.001$). The differences in spectral measures of HR variability were consistent during the daytime and during different phases of sleeping hours (Table).

**Middle-Aged and Elderly Versus Young Subjects**

A linear decrease of ApEn ($r=-0.69$) and $\beta$ ($r=0.60$) and an increase in $\alpha_2$ ($r=0.63$) with age occurred during middle age
Measures of 24-Hour R-R Interval Dynamics in Healthy Children and Young, Middle-Aged, and Elderly Subjects (n=114)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Children, &lt;15 y (n=27)</th>
<th>Young Adults, 15–39 y (n=29)</th>
<th>Middle-Aged, 40–60 y (n=29)</th>
<th>Elderly, &gt;60 y (n=29)</th>
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<td>8±5</td>
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<td>876±88</td>
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<td>71±5</td>
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<tr>
<td>28±6</td>
<td>678±105*</td>
<td>825±161*</td>
<td>614±91*</td>
<td>519±65</td>
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<td>50±6</td>
<td>678±121</td>
<td>1074±117</td>
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<td>118±33*</td>
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<td>6.83±1.12</td>
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<td>6.10±0.72†</td>
<td>5.06±0.61*</td>
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<td>5.55±0.76†</td>
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<td>β</td>
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<tr>
<td>24-h</td>
<td>−1.15±0.18</td>
<td>−1.12±0.19</td>
<td>−1.32±0.14†</td>
<td>−1.38±0.17‡</td>
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<td>1.19±0.14</td>
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<td>9 AM–6 PM</td>
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<td>1.01±0.21</td>
<td>1.13±0.21</td>
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<td>c2</td>
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<td>0.98±0.06</td>
<td>1.00±0.08</td>
<td>1.07±0.07†</td>
<td>1.14±0.07*</td>
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<tr>
<td>9 AM–6 PM</td>
<td>0.96±0.10§</td>
<td>0.99±0.10</td>
<td>1.06±0.10</td>
<td>1.12±0.11</td>
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<td>ApEn</td>
<td>0.95±0.10</td>
<td>0.98±0.09</td>
<td>1.06±0.08†</td>
<td>1.12±0.10‡</td>
</tr>
</tbody>
</table>

SDNN indicates standard deviation of R-R intervals; HF, high-frequency power; ln, natural logarithm of the absolute value in ms<sup>2</sup>; LF, low-frequency power; VLF, very-low-frequency power; ULF, ultralow-frequency power; β, slope of power-law relationship of HR variability; c1, short-term scaling exponent; c2, intermediate-term scaling exponent; and ApEn, approximate entropy. Values are mean±SD.

Symbols express the difference between groups in 1-way ANOVA followed by Bonferroni post hoc analysis with a confidence level of P<0.05.

*Group differed from 3 other groups.
†Middle-aged differed from children and young adults.
‡Elderly differed from children and young adults.
§Children differed from middle-aged and elderly.
||Group differed from young adults and middle-aged.
and old age ($P<0.001$ for all) (Figure 5, Table). Middle-aged and elderly subjects had significantly lower values for $\beta$ and ApEn and higher values for $\alpha_1$ than the 2 younger groups (Table). The short-term scaling exponent, $\alpha_1$, did not differ among the 3 adult groups. A decrease of all time- and frequency-domain measures also occurred with age in adults (Table). Differences in various indices between the age groups were similar during the daytime and the nighttime (Table).

To determine whether a decrease in total HR variability explains the changes in dynamic measures of R-R interval variability with increasing age, an ANCOVA was performed using SDNN and age group as explanatory variables and each of the 4 dynamic measures of R-R interval variability as a dependent variable. The significant differences for ApEn, $\beta$, $\alpha_1$, and $\alpha_2$ between the groups still remained after adjustment for SDNN ($P<0.001$ for each).

**Day-Night Differences**

In all age groups, ApEn was higher ($P<0.001$ in each group), $\alpha_1$ was lower ($P<0.001$ in children and young adults, $P<0.05$ in middle-aged and elderly), and all spectral measures were higher ($P<0.01$ for all in each group) during sleep times than daytime (Table).

**Effects of Sex on R-R Interval Dynamics**

$\alpha_1$ was significantly lower ($1.10 \pm 0.13$ versus $1.18 \pm 0.16$, $P<0.01$), $\beta$ was slightly steeper ($-1.29 \pm 0.21$ versus $-1.21 \pm 0.19$, $P<0.05$), and VLF was slightly lower ($7.14 \pm 0.70$ versus $7.45 \pm 0.78$, $P<0.05$) in females, whereas no other differences were observed compared with males. Similar age dependencies of the different measures of R-R interval dynamics were observed in both males and females.

**Discussion**

The results of this study indicate that R-R interval dynamics change markedly from childhood to old age in healthy subjects. However, there are important age-related differences among various measures. Children show complexity and fractal correlation properties of R-R interval dynamics comparable to those of young, healthy adults despite lower overall HR variability. Progressive loss of complexity (increased regularity and predictability) and a decrease in total variability of R-R intervals occur from middle age to old age. Of particular note, the observed reduction in complexity and the changes in the fractal correlation properties with aging were not accompanied by a reduction in overall HR variability. Thus, dynamic measures of R-R interval variability provide complementary information about HR behavior when used in concert with traditional time- and frequency-domain HR variability measures.

**Dynamic Analysis of R-R Intervals**

The mathematical basis for new dynamic measures of R-R interval variability used in this study has been described elsewhere.\(^{11,13–19}\) Briefly, ApEn describes the predictability or complexity of time-series data.\(^{17–19}\) the slope of the power-law relationship describes the fractal-like correlation properties of R-R interval data over long time periods.\(^{13–15}\) and $\alpha_1$ and $\alpha_2$ describe the correlation properties of the short-term and intermediate-term R-R interval fluctuation, respectively.\(^{11,16}\)

**R-R Interval Dynamics During Childhood**

In this study, the complexity (ApEn) and temporal correlation properties of HR behavior ($\alpha_1$, $\alpha_2$, and $\beta$) in children were similar to those of young adults. Both children and young adults showed R-R interval dynamics with $1/f$ behavior ($\alpha_1$ and $\alpha_2 \approx 1.0$, $\beta \approx -1.0$), consistent with a system with fractal-like, scale-invariant correlations. To the best of our knowledge, this is the first study to analyze these dynamic measures of R-R intervals in children. Our findings also confirm the reduced frequency-domain measures in young children versus young adults observed in previous studies.\(^{1,2}\)

**R-R Interval Dynamics During Adult Life: Effect of Increasing Age**

A steeper $\beta$ (the slope of the power-law relationship), a decrease of ApEn (complexity), and an increase of $\alpha_2$ (the intermediate-term scaling exponent) were observed with increasing age, suggesting that the longer-term R-R interval dynamics change from $1/f$ behavior toward $1/f^2$ behavior. These findings are consistent with lower complexity (higher regularity and predictability) of R-R interval dynamics with increasing age. All traditional measures of HR variability also decrease with aging, evidenced by lower total variance and smaller spectral power at all frequencies. These observations are consistent with previous findings showing decreased total variance,\(^{3–6}\) decreased spectral power of VLF, LF, and HF,\(^{7}\) steeper slopes of the power-law relationship,\(^{6}\) and reduced ApEn values\(^{8,12}\) with old age.

**Day-Night Difference of the Different Measures**

The findings of increased ApEn, decreased $\alpha_1$, and increased spectral components during nighttime indicate increased variance and complexity of HR dynamics at night. The age dependence of different measures of R-R interval dynamics were similar when analyzed from 24 hours or from nighttime hours. Thus, differences in physical activity among different age groups (children versus elderly) during daytime do not explain the observed age-related changes in R-R interval dynamics.

**Effects of Sex on R-R Interval Dynamics**

Previous studies using short-term ECG recordings under controlled breathing and activity conditions have reported increased complexity (ApEn)\(^{12}\) and lower LF and higher HF\(^{20}\) in women compared with men. In the present study, women had significantly lower $\alpha_1$ than men, whereas other measures did not differ. Thus, in women, short-term R-R interval dynamics seem to be closer to $1/f$ behavior than in men.

**Interpretation of Age-Related Differences in R-R Interval Dynamics**

It has been suggested that scale invariance may be a central organizing principle of physiological structure and function. The breakdown of this scale-invariant, fractal organization could lead to either totally uncorrelated randomness or highly
predictable (single-scale) behavior, both of which may result in a less adaptable system.\textsuperscript{10} Thus, changes from 1/f scale-invariant behavior toward behavior resembling either random fluctuations (white noise) or toward 1/f\textsuperscript{2} behavior with less complexity might be physiologically deleterious. These changes seem to occur with physiological aging. In contrast, children already show a “mature”-pattern R-R interval dynamics comparable to that of healthy young adults, with complex, fractal dynamics suggesting a highly adaptive cardiovascular regulatory system.

The age-related changes in different measures of R-R interval dynamics are probably a marker of the various physiological mechanisms affecting these measures, especially neuroauntomatic inputs.\textsuperscript{13,23} The finding that children showed a similar slope of the power-law relationship of R-R interval dynamics compared with young adults, despite reduced power of various spectral components, indicates that these indexes are differentially regulated and that HR variance and related measures cannot be used as surrogates for complexity measures.

Limitations of the Study

Twenty-four-hour recordings have been recommended for HR variability testing in various cardiovascular disorders because of better reproducibility of long-term versus short-term recordings.\textsuperscript{24} The purpose of the present study was to examine the R-R interval dynamics of 24-hour recordings of healthy subjects during normal “free-running” conditions, recognizing potential confounding effects of nonstationarities due to diurnal rhythms, activity, and other factors. Because standardized conditions (eg, controlled breathing, body posture, and physical activity) were not used, this study cannot provide an exact physiological basis for differences in various measures of R-R interval dynamics between the age groups. New fractal and complexity-related measures of HR variability can be reliably analyzed only from relatively long recording periods (several hours). It is not practicable to standardize external conditions for such a long period of time, particularly in children. Therefore, we also analyzed separately the various indices of HR variability during the early phase of sleeping hours, which should partly standardize the level of physical activity and the type of sleep.\textsuperscript{25}

Implications

Newer dynamic measures of fractal-like properties of R-R interval variability complement traditional time- and frequency-domain measures of HR variability. These novel methods may uncover hidden abnormalities or alterations in time-series data.\textsuperscript{6} For example, the slope, $\beta$, of the power-law relationship has been reported to be a stronger predictor of mortality after myocardial infarction\textsuperscript{13} and in a general elderly population\textsuperscript{15} than conventional spectral measures of HR variability. Similarly, fractal measures of HR dynamics have prognostic value as independent predictors of survival in patients with depressed left ventricular function after acute myocardial infarction\textsuperscript{26} and in heart failure,\textsuperscript{27} of vulnerability to life-threatening arrhythmia,\textsuperscript{28} and in distinguishing subjects with coronary artery disease from healthy control subjects.\textsuperscript{29} The findings of the present study may be useful in quantifying and modeling\textsuperscript{30} changes in the complex, nonlinear functioning of the healthy cardiovascular system in relation to age. Finally, age dependence of different measures of R-R interval dynamics must be taken into account when normal reference values of these measures are given for different subsets of subjects.

Acknowledgments

This work was supported by grants from the Finnish Foundation for Cardiovascular Research, Helsinki, Finland; the Ida Montin Foundation, Helsinki, Finland; the National Aeronautics and Space Administration, Washington, DC; the National Institute of Mental Health, Bethesda, Md; the G. Harold and Leila Y. Mathers Charitable Foundation, Mt Kisco, New York; and the Finnish Life and Pension Insurance Companies, Helsinki, Finland. The authors thank Jeff Hausdorff, PhD, for helpful suggestions.

References


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_Circulation_. 1999;100:393-399
doi: 10.1161/01.CIR.100.4.393
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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