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, β, of the power-law regression line (log power−log frequency) of R-R interval variability (10^{-4} to 10^{-2} Hz), approximate entropy (ApEn), short-term (α_1) and intermediate-term (α_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 (α_1, α_2, β) of R-R interval dynamics despite lower spectral and time-domain measures. Progressive loss of complexity (decreased ApEn, $r=-0.69$, $P<0.001$) and alterations of long-term fractal-like heart rate behavior (increased α_2, $r=0.63$, decreased β, $r=-0.60$, $P<0.001$ 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 variability[2–7] 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

Received February 1, 1999; revision received April 21, 1999; accepted April 30, 1999.

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interval dynamics. Reduced HR variability and loss of HR complexity have been reported with increasing age.[2–8,11,12] However, previous studies have important limitations related to analyses based solely on traditional time- and frequency-domain measures,[2–5,7] on short-term (<3 hours) ECG recordings,[6,11,12] or on comparisons between small groups with widely disparate ages but without including children.[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[13–15] and detrended fluctuation analysis (DFA),[11,16] and approximate entropy (ApEn),[17–19] a "complexity" measure.

Methods

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 years); (2) young adults, 15 to 40 years old (mean, 28±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[20] and elderly subjects[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 a 12-lead ECG with the Minnesota code) 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.

HR Recordings

A 24-hour ambulatory ECG recording was performed during usual everyday activities. All subjects had ≥18 hours (mean, 23±1 hours) of ECG data, including ≥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.[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.

HR Variability Measures

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.

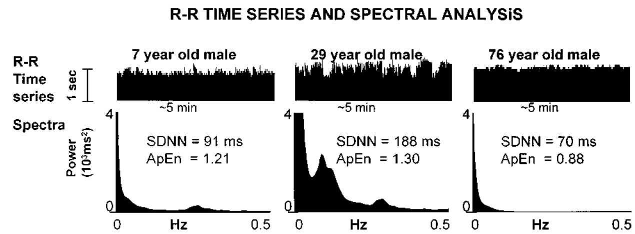

Figure 1. Representative examples of R-R interval time series and 24-hour power spectra of 7-year-old (left), 29-year-old (middle), and 76-year-old (right) healthy males. Abbreviations as in Table.

Fractal Scaling and Complexity Measures: Power-Law Relationship Analysis

The slope, β, of the power spectrum was calculated as described previously[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.[13]

DFA quantifies fractal-like correlation properties of the time-series data.[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 α represents the slope of this line, which relates (log)fluctuation to (log)window size. In this study, both α_1, the short-term (4 to 11 beats) and α_2, 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,[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.[17–19] In addition, α_1, α_2, 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.

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.

Results

Representative examples of R-R interval time-series, 24-hour power-spectra, power-law, and scaling DFAs 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.

Children Versus Young Adults

Measures of complexity (ApEn) and short-term (α_1) and longer-term temporal correlation properties (α_2 and β) of R-R intervals did not differ between children and young adults

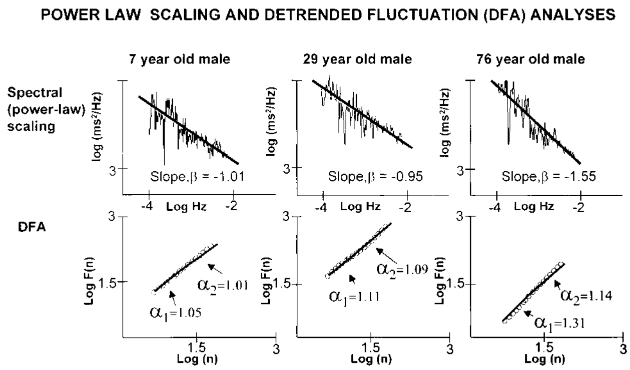

Figure 2. Representative examples of power-law relationship analyses and DFAs of 7-year-old (left), 29-year-old (middle), and 76-year-old (right) healthy males. Abbreviations as in Table.

(Table). 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, α_1, and β 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), α_1 (0.88±0.19 versus 1.00±0.21, P=NS), or α_2 (0.92±0.11 versus 0.95±0.1.0, 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).

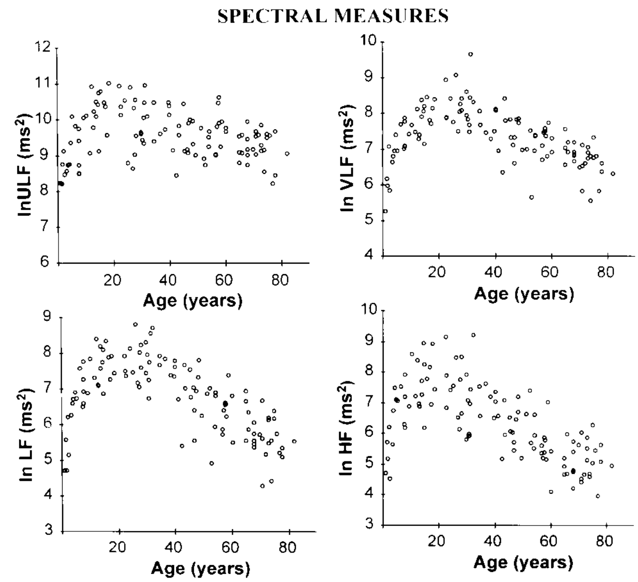

Figure 4. Frequency-domain measures of HR variability in relation to age in 114 healthy subjects. Abbreviations as in Table.

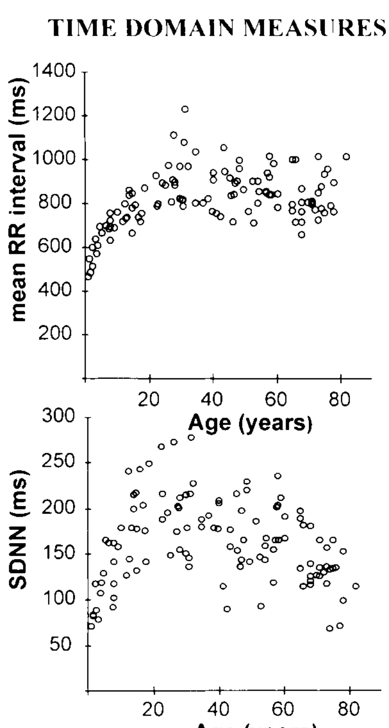

Figure 3. Time-domain measures of HR variability in relation to age in 114 healthy subjects. Abbreviations as in Table.

Middle-Aged and Elderly Versus Young Subjects

A linear decrease of ApEn ($r=-0.69$) and β ($r=0.60$) and an increase in α_2 ($r=0.63$) with age occurred during middle age

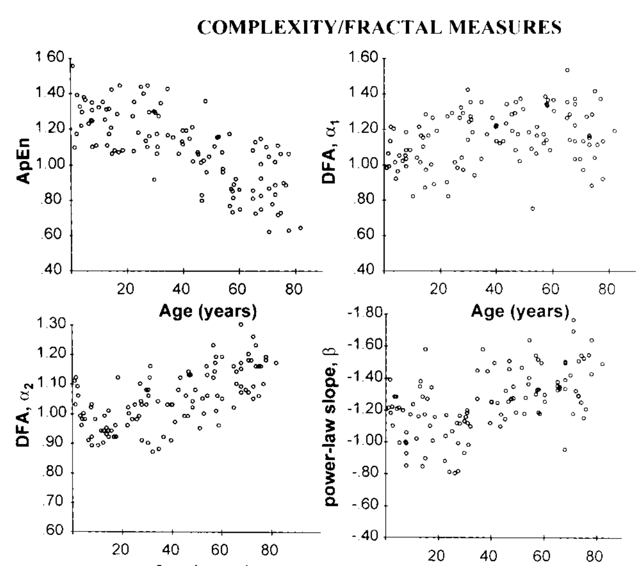

Figure 5. Measures of complexity and fractal scaling of R-R interval dynamics in relation to age in 114 healthy subjects. Abbreviations as in Table.

Measures of 24-Hour R-R Interval Dynamics in Healthy Children and Young, Middle-Aged, and Elderly Subjects (n=114)

	Children, <15 y (n=27)	Young Adults, 15–39 y (n=29)	Middle-Aged, 40–60 y (n=29)	Elderly, >60 y (n=29)
Age, y	8±5	28±6	50±6	71±5
Traditional time and frequency-domain measures				
Mean R-R interval, ms				
24-h	678±105*	875±121	876±88	829±96
Midnight–6 AM	825±161*	1074±117	1050±127	954±119
9 AM–6 PM	614±91*	811±146	796±81	730±168
SDNN, ms				
24-h	140±46‖	196±39	169±39	138±32‖
Midnight–6 AM	95±41	135±36*	92±28	73±16
9 AM–6 PM	80±23	118±33*	98±21	76±18
HF, ln				
24-h	6.83±1.12	7.35±0.94	6.10±0.72†	5.06±0.61*
Midnight–6 AM	7.27±1.35	7.82±0.97	6.51±0.89†	5.27±0.73*
9 AM–6 PM	6.20±1.03	6.69±1.04	5.55±0.76†	4.77±0.59*
LF, ln				
24-h	6.85±0.97	7.74±0.50*	6.66±0.74	5.73±0.63*
Midnight–6 AM	7.03±1.09	7.98±0.55*	6.90±0.93	6.01±0.73*
9 AM–6 PM	6.66±0.98	7.49±0.65*	6.44±0.66	5.39±0.65*
VLF, ln				
24-h	7.19±0.75	8.07±0.53*	7.30±0.58	6.72±0.45*
Midnight–6 AM	7.60±0.76	8.52±0.39*	7.84±0.71	7.17±0.48*
9 AM–6 PM	7.05±0.67	7.90±0.62*	7.22±0.59	6.46±0.51*
ULF, ln				
24-h	9.39±0.81	10.02±0.66*	9.54±0.56	9.25±0.43*
Fractal scaling/complexity measures				
β				
24-h	−1.15±0.18	−1.12±0.19	−1.32±0.14†	−1.38±0.17‡
α_1				
24-h	1.06±0.11§	1.15±0.16	1.19±0.14	1.19±0.16
Midnight–6 AM	0.91±0.18§	1.01±0.21	1.13±0.21	1.26±0.20
9 AM–6 PM	1.13±0.13	1.20±0.16	1.24±0.14	1.15±0.16
α_2				
24-h	0.98±0.06	1.00±0.08	1.07±0.07†	1.14±0.07*
Midnight–6 AM	0.96±0.10§	0.99±0.10	1.06±0.10	1.12±0.11
9 AM–6 PM	0.95±0.10	0.98±0.09	1.06±0.08†	1.12±0.10‡
ApEn				
24-h	1.26±0.12	1.21±0.14	1.01±0.16†	0.88±0.16*
Midnight–6 AM	1.37±0.13	1.34±0.19	1.27±0.17	1.06±0.15*
9 AM–6 PM	1.18±0.14	1.12±0.12	0.98±0.13†	0.91±0.17‡

SDNN indicates standard deviation of R-R intervals; HF, high-frequency power; ln, natural logarithm of the absolute value in ms^2; LF, low-frequency power; VLF, very-low-frequency power; ULF, ultralow-frequency power; β, slope of power-law relationship of HR variability; α_1, short-term scaling exponent; α_2, 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 β and ApEn and higher values for α_2 than the 2 younger groups (Table). The short-term scaling exponent, α_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, β, α_1, and α_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), α_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

α_1 was significantly lower (1.10 ± 0.13 versus 1.18 ± 0.16, $P<0.01$), β was slightly steeper (-1.29 ± 0.21 versus -1.21 ± 0.19, $P<0.05$), and VLF was slightly lower (7.14 ± 0.70 versus 7.45 ± 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 α_1 and α_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 (α_1, α_2, and β) in children were similar to those of young adults. Both children and young adults showed R-R interval dynamics with 1/f behavior (α_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 β (the slope of the power-law relationship), a decrease of ApEn (complexity), and an increase of α_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 α_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 α_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.[10] Thus, changes from 1/f scale-invariant behavior toward behavior resembling either random fluctuations (white noise) or toward $1/f^2$ 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 neuroautonomic inputs.[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.[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.[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.[6] For example, the slope, β, of the power-law relationship has been reported to be a stronger predictor of mortality after myocardial infarction[13] and in a general elderly population[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[26] and in heart failure,[27] of vulnerability to life-threatening arrhythmia,[28] and in distinguishing subjects with coronary artery disease from healthy control subjects.[29] The findings of the present study may be useful in quantifying and modeling[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

1. Finley JP, Nugent ST. Heart rate variability in infants, children and young adults. *J Auton Nerv Syst*. 1995;51:103–108.
2. Korkushko OV, Shatilo VB, Plachinda YuI, Shatilo TV. Autonomic control of cardiac chronotropic function in man as a function of age: assessment by power spectral analysis of heart rate variability. *J Auton Nerv Syst*. 1991;32:191–198.
3. Hellman JB, Stacy RW. Variation of respiratory sinus arrhythmia with age. *J Appl Physiol*. 1976;41:734–738.
4. O'Brien IAD, O'Hare P, Corrall RJM. Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function. *Br Heart J*. 1986;55:348–354.
5. Shannon DC, Carley DW, Benson H. Aging of modulation of heart rate. *Am J Physiol*. 1987;253:H874–H877.
6. Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt: relations to aging and risk of syncope. *Circulation*. 1990;81:1803–1810.
7. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Schneider WJ, Stein PK. RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation*. 1995;91:1936–1943.
8. Kaplan DT, Furman MI, Pincus SM, Ryan SM, Lipsitz LA, Goldberger AL. Aging and the complexity of cardiovascular dynamics. *Biophys J*. 1991;59:945–949.
9. Lipsitz LA, Goldberger AL. Loss of "complexity" and aging: potential applications of fractals and chaos theory to senescence. *JAMA*. 1992;267:1806–1809.
10. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet*. 1996;347:1312–1314.
11. Iyengar N, Peng CK, Morin R, Goldberger AL, Lipsitz LA. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *Am J Physiol*. 1996;271:R1078–R1084.
12. Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender- and age-related differences in heart rate dynamics: are women more complex than men? *J Am Coll Cardiol*. 1994;24:1700–1707.
13. Bigger JT Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation*. 1996;93:2142–2151.
14. Goldberger AL, West BJ. Fractals in physiology and medicine. *Yale J Biol Med*. 1987;60:421–435.
15. Huikuri HV, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Puukka P, Räihä IJ, Sourander LB. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation*. 1998;97:2031–2036.
16. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *CHAOS*. 1995;5:82–87.
17. Pincus SM, Viscarello RR. Approximate entropy: a regularity measure for fetal heart rate analysis. *Obstet Gynecol*. 1992;79:249–255.
18. Pincus, SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify? *Am J Physiol*. 1994;266:H1643–H1656.

19. Mäkikallio TH, Seppänen T, Niemelä M, Airaksinen KEJ, Tulppo M, Huikuri HV. Abnormalities in beat to beat complexity of heart rate dynamics in patients with a previous myocardial infarction. *J Am Coll Cardiol*. 1996;28:1005–1011.
20. Huikuri HV, Pikkujämsä SM, Airaksinen KEJ, Ikäheimo MJ, Rantala AO, Kauma H, Lilja M, Kesäniemi YA. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. *Circulation*. 1996;94:122–125.
21. Räihä IJ, Piha SJ, Seppänen A, Puukka P, Sourander LB. Predictive value of continuous ambulatory electrocardiographic monitoring in elderly people. *BMJ*. 1994;309:1263–1267.
22. Huikuri HV, Niemelä MJ, Ojala S, Rantala A, Ikäheimo MJ, Airaksinen KEJ. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease: effects of arousal and upright posture. *Circulation*. 1994;90:121–126.
23. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol*. 1985;249:H867–H875.
24. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996;93:1043–1065.
25. Kales A, Kales JD. Sleep disorders: recent findings in the diagnosis and treatment of disturbed sleep. *N Engl J Med*. 1974;290:487–499.
26. Mäkikallio TH, Hoiber S, Kober L, Torp-Pedersen C, Peng CK, Goldberger AL, Huikuri HV. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after myocardial infarction. *Am J Cardiol*. 1999;83:836–839.
27. Ho KKL, Moody GB, Peng CK, Mietus JE, Larson MG, Levy D, Goldberger AL. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. *Circulation*. 1997;96:842–848.
28. Mäkikallio TH, Seppänen T, Airaksinen KEJ, Koistinen J, Tulppo MS, Peng CK, Goldberger AL, Huikuri HV. Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. *Am J Cardiol*. 1997;80:779–783.
29. Mäkikallio TH, Ristimäe T, Airaksinen KEJ, Peng CK, Goldberger AL, Huikuri HV. Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. *Am J Cardiol*. 1998;81:27–31.
30. Ivanov PC, Amaral LAN, Goldberger AL, Stanley HE. Stochastic feedback and the regulation of biological rhythms. *Europhys Lett*. 1998;43:363–368.