Heart Rate Dynamics Before Spontaneous Onset of Ventricular Fibrillation in Patients With Healed Myocardial Infarcts

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The traditional methods of analyzing heart rate (HR) variability have failed to predict imminent ventricular fibrillation (VF). We sought to determine whether new methods of analyzing RR interval variability based on nonlinear dynamics and fractal analysis may help to detect subtle abnormalities in RR interval behavior before the onset of life-threatening arrhythmias. RR interval dynamics were analyzed from 24-hour Holter recordings of 15 patients who experienced VF during electrocardiographic recording. Thirty patients without spontaneous or inducible arrhythmia events served as a control group in this retrospective case control study. Conventional time- and frequency-domain measurements, the short-term fractal scaling exponent (α) obtained by detrended fluctuation analysis, and the slope (β) of the power-law regression line (log power − log frequency, 10^{-4} −10^{-2} Hz) of RR interval dynamics were determined. The short-term correlation exponent α of RR intervals (0.64 ± 0.19 vs 1.05 ± 0.12; p <0.001) and the power-law slope β (−1.63 ± 0.28 vs −1.31 ± 0.20, p <0.001) were lower in the patients before the onset of VF than in the control patients, but the SD and the low-frequency spectral components of RR intervals did not differ between the groups. The short-term scaling exponent performed better than any other measurement of HR variability in differentiating between the patients with VF and controls. Altered fractal correlation properties of HR behavior precede the spontaneous onset of VF. Dynamic analysis methods of analyzing RR intervals may help to identify abnormalities in HR behavior before VF. ©1999 by Excerpta Medica, Inc.

(Am J Cardiol 1999;83:880–884)

The risk of life-threatening arrhythmias after acute myocardial infarction has been shown to be increased in patients with reduced heart rate (HR) variability.[1–5] Controversial information has been available on possible abnormalities in HR behavior before the spontaneous onset of ventricular fibrillation (VF),[6–8] however. Although the traditional methods of HR variability analysis have failed to predict imminent VF,[6] there are a variety of new methods available for measuring the complex (usually nonlinear) behavior of dynamic processes.[9–17] These methods may detect subtle abnormalities in RR interval dynamics and complement the traditional methods of analyzing HR variability in various patient populations.[18–20] Our general goal was to test the hypothesis that methods of analysis based on nonlinear dynamics ("chaos theory") and fractals can reveal abnormalities in HR behavior before the onset of VF in postinfarction patients.

METHODS

Subjects: The VF group in the present case-controlled analysis consisted of 10 patients retrospectively identified from the Oulu University Hospital Holter measurement database, all of whom had had a spontaneous onset of VF during 24-hour electrocardiographic recording without significant preceding ST-segment changes, and who had undergone electrophysiologic and angiographic examinations. All of these patients had been referred for examinations because of a recent clinical history of a life-threatening arrhythmic event, and had experienced a recurrent VF event before or after the invasive electrophysiologic and angiographic examinations in the hospital. Holter recordings had been performed as part of the routine examinations of these patients. Three of the episodes started as primary VF, 3 as fast monomorphic ventricular tachycardia, and 4 as polymorphic ventricular tachycardia degenerating into VF. Two patients died from VF and 8 were successfully resuscitated by direct-current shock. The postinfarction control group consisted of 20 patients with a history of Q-wave myocardial infarction (>1 month since infarction), but without a history of ventricular arrhythmia events. These patients were selected from among 83 consec-

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0002-9149/99/$–see front matter
PII S0002-9149(98)01068-6

utive patients with a prior myocardial infarction referred for angiography due to angina pectoris or for prognostic reasons, and who underwent programmed electrical stimulation. Patients with inducible nonsustained (>5 consecutive beats) or sustained ventricular tachyarrhythmia, diabetes mellitus, or atrial fibrillation were excluded. The patients with VF were matched with the postinfarction controls with respect to age, sex, left ventricular ejection fraction, β blocker and diuretic medication, and functional class. The matched parameters were scaled as follows: (1) age matching as per 5 years (between 55 and 60 years, between 60 and 65 years, between 65 and 70 years, between 70 and 75 years, and between 75 and 80 years), (2) male or female gender, (3) left ventricular ejection fraction <30%, between 30% and 40%, between 40% and 50%, or >50%, (4) and (5) medication, and (6) New York Heart Association classes I to IV. Two postinfarction control subjects who had had an arrhythmia-free follow-up period of 2 years were matched to each patient in the VF group.

Due to the relatively small patient population, 5 additional patients with VF during a Holter recording were also studied: 3 from the Ghent University Hospital, 1 from the records of GW Scientific Inc, Rowayton, Connecticut, and 1 from the Oulu University Hospital, for whom detailed clinical and angiographic data were not available. Two additional postinfarction age- and sex-matched control subjects were matched to each patient with VF in this expanded patient group.

Electrophysiologic and angiographic examinations: Electrophysiologic testing included incremental ventricular pacing and programmed ventricular stimulation using up to 3 extra stimuli and 2 basic drive cycle lengths (600 and 400 ms) from the right ventricular apex and the outflow tract. The stimulation protocol and the definition of induced ventricular arrhythmia have been previously described in detail.[21] Left heart catheterization was performed by Judkins' technique on all control patients within 2 months of the electrocardiographic recordings. These tests were performed on all postinfarction control patients and all of the patients in the VF group, but not on the 5 patients with VF in the expanded group.

Heart rate variability measurements: The postinfarction control subjects were monitored for 24 hours with an ambulatory electrocardiographic recorder (Dynacord Holter Recorder, model 420, DM Scientific, Irvine, California), and the data were sampled digitally and transferred from the Delmar Avionics Scanner (Delmar Avionics, Irvine, California) to a microcomputer for the analysis of HR variability. The details of this analysis technique have been described previously.[21,22] Briefly, the RR interval series were edited manually and premature beats and noise were deleted. Questionable portions were printed out on a 2-channel electrocardiogram at a paper speed of 25 mm/s to confirm the sinus origin of the RR interval data. HR variability measurements over the same period and with a similar length of electrocardiographic recording were obtained for the control patients for comparison. The average length of electrocardiographic recordings per patient with VF was 16 ± 6 hours (range 6 to 24).

An autoregressive model was used to estimate the power spectrum densities of RR interval variability.[22,23] The power spectra were quantified by measuring the area in 3 frequency bands: 0.005 to 0.04 Hz (very low frequency), 0.04 to 0.15 Hz (low frequency), and 0.15 to 0.40 Hz (high frequency). The SD and mean length of the RR intervals were used as time-domain measurements.

Power-law scaling of RR interval variability was calculated over the frequency range 10^{-4} to 10^{-2} Hz. A robust line-fitting algorithm of log (power) on log (frequency) was applied to the power spectrum between 10^{-4} to 10^{-2} Hz, and the slope of this line was calculated (β). This frequency band was chosen on the basis of previous observations regarding the linear relation between log (power) and log (frequency) in this frequency band.[24,25]

The detrended fluctuation analysis technique was used to quantify fractal scaling properties of RR interval data.[12,13] The root-mean-square fluctuation of integrated and detrended time series was measured at each observation window and plotted against the size of the observation window on a log–log scale. In this method, the fractal-like signal (1/f signal spectrum) results in exponent value 1 ($\alpha = 1.0$). The white Gaussian noise (random signal) results in value 0.5 ($\alpha = 0.5$) and the Brownian noise signal ($1/f^2$ signal spectrum) in exponent value 1.5. The present HR correlations were defined for short-term (<11 beats, α) RR interval data, based on a previous finding of altered short-term fractal HR behavior among arrhythmic patients.[20] The short-term fractal exponent was computed from segments of 4,000 consecutive RR intervals and averaged to obtain mean values for the entire recording period.

The effect of the number of excluded beats (data editing) on detrended fluctuation analysis was studied by progressively increasing the number of deleted beats from the same data set. The short-term scaling exponent did not change significantly if <20% of the beats were randomly excluded. The effect of the number of existing premature beats on scaling exponents was studied by adding and increasing progressively short- and long-term intervals into artificially generated RR interval data. Scaling exponent decreased in relation to added premature beats. The effect was minimal when <100 premature beats per hour were randomly added (<5% difference), but the exponent decreased progressively when >100 premature beats per hour were included in the analysis, indicating that the differences between the groups would be even greater without excluding premature beats than the traditional way performed in the present study.

Statistical analysis: The results are given as means ± SD unless otherwise indicated. Because of the skewness of the data, the Mann-Whitney U test was performed to analyze the differences between the groups. The paired *t* test for dependent variables was used to analyze the differences before the fibrillation and in the 24-hour average. Stepwise multiple regres-

TABLE I Characteristics of the Study Groups

	VF Group (n = 10)	MI Control group (n = 20)
Clinical data		
Age (yrs)	67 ± 4	65 ± 4
NYHA class		
III–IV	10	20
Time since prior MI (mo)	20 ± 27	50 ± 63
Location of prior MI		
Anterior	4	7
Inferior	1	6
Anterior + inferior	5	7
Angiographic data		
1-vessel disease	0	1
2-vessel disease	2	6
3-vessel disease	8	13
Ejection fraction (%)	38 ± 8	44 ± 9
VPC class*		
1 (<10 VPCs/h)	0	13
2 (10–30 VPCs/h)	3	3
3 (>30 VPCs/h)	7	4
NSVT on Holter	8*	4
Cardiac medication		
Digitalis	8	9
Diuretic	7	15
β blocker	6	12
Calcium antagonist	4	5
ACE inhibitor	6	8

*p <0.01, significance levels for differences between the VF group and their controls in analysis of variance.

Values are mean ± SD.

ACE = angiotensin-converting enzyme; MI = myocardial infarction; NYHA = New York Heart Association; VPC = ventricular premature complex.

sion analysis was used to determine the best independent variable when differentiating between the patient groups (SPSS for Windows Release 6.1.3., Chicago, Illinois). A p value <0.05 was considered significant.

RESULTS

Clinical, angiographic, and electrophysiologic data: The clinical and angiographic data are presented in Table I. Neither sustained nor nonsustained ventricular arrhythmia could be induced in any of the postinfarction control patients by the study design. Eight of the 10 patients with spontaneous VF were inducible into sustained ventricular tachyarrhythmia during the programmed electrical stimulation. The frequency of ventricular premature depolarizations and the occurrence of nonsustained ventricular tachycardia on the Holter recordings were significantly higher in the patients with VF compared with the postinfarction control subjects.

RR interval variability: Two examples of electrocardiographic recordings before the spontaneous onset of VF are shown in Figure 1. Figure 2 displays the RR interval tachogram and HR behavior measurements before the spontaneous onset of VF (left column, patient B in Figure 1). The reduced short-term fractal exponent α was typically seen in RR interval dynamics before the VF episodes. In contrast, the control patients typically had a normal fractal short-term HR behavior (right column, $\alpha \sim 1.0$, Figure 2).

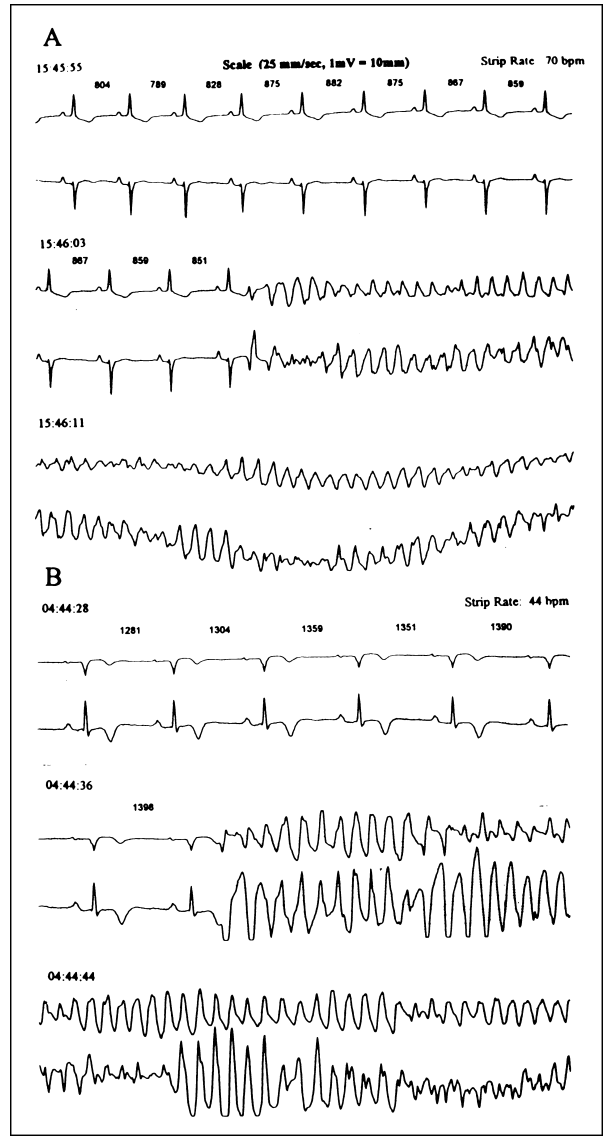

FIGURE 1. ***A and B,*** **2 different examples of electrocardiographic recordings before the onset of VF.**

The average HR did not differ significantly between the patients with VF and their controls, but there was a clear tendency toward higher HRs among the patients with VFs. The SD of RR intervals, very-low-frequency, and low-frequency spectral components did not differ significantly between the groups, but the high-frequency spectral component was somewhat higher in the patients with VF ($p < 0.05$). The short-term fractal-related scaling exponent α and the power-law regression slope β showed smaller values in the VF group than in postinfarction control group ($p < 0.001$ and $p < 0.01$, respectively, see Figure 2, Table II).

In stepwise multiple regression analysis, including the ventricular premature depolarization frequency, the occurrence of nonsustained ventricular tachycardia, detrended fluctuation analysis, power-law behavior analysis of low frequencies, and conventional time- and frequency-domain measurements of HR

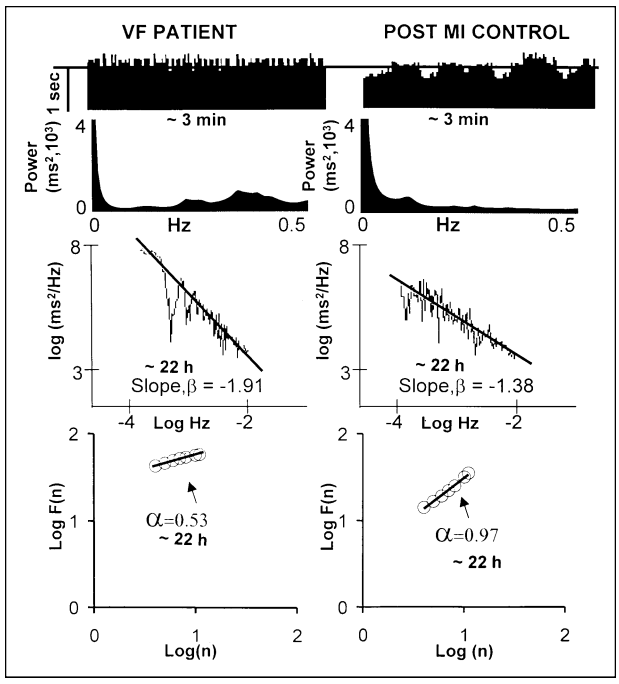

FIGURE 2. Examples of RR interval tachograms *(upper panels)*, power spectrums *(upper middle panels)*, power-law slopes *(middle lower panels)* of RR intervals, and detrended fluctuation analyses *(lower panels)* preceding the spontaneous VF of 1 patient (*left column*, the electrocardiographic recording shown in Figure 1B). This patient shows a widened high-frequency spectral band, a steep power-law slope, and a reduced short-term scaling exponent ($\alpha \sim 0.5$). A representative postinfarction control patient without arrhythmia during the recording or during a follow-up of 2 years afterwards shows fractal short-term exponent value $\alpha \sim 1.0$ *(right column)*. α = short-term scaling exponent; β = power-law scaling slope; MI = myocardial infarction.

variability, the short-term fractal-like scaling exponent proved to be the most powerful independent predictor differentiating the patients with VF from the postinfarction controls ($\beta = -37.5$, $p < 0.001$). None of the variables changed significantly during the last hour or 15 minutes before the spontaneous onset of VF compared with the longer period preceding VF. The results were quite similar when a comparison was made between the expanded VF group (n = 15) and their matched controls. The faster average HR in the patients VF than in the controls reached statistical significance (Table III).

DISCUSSION

The major new finding of this study was that specific abnormalities in the dynamic behavior of RR interval dynamics was observed before the spontaneous onset of VF. Furthermore, the new analysis methods of RR intervals based on nonlinear dynamics ("chaos theory") and fractals can identify these abnormalities in HR behavior preceding VF that are not detectable by traditional time- and frequency-domain methods. Consistent with these findings, Vybiral et al[5] have shown that the conventional analysis of HR variability fails to predict imminent VF, whereas Skinner et al[16] observed changes in the nonlinear correlation dimension of RR intervals several hours before the onset of VF.

Altered beat to beat RR interval dynamics were also found to precede the onset of VF, using analysis of fractal scaling based on detrended fluctuation analysis and 1/f scaling analysis. Detrended fluctuation analysis showed that the altered beat to beat RR interval variability resulted from an almost random-like form of short-term RR interval behavior (0.67 observed average of α vs 0.5 predicted for completely random behavior) rather than the fractal-like correlation properties ($\alpha \sim 1.0$) previously observed in uncomplicated postinfarction control patients and in healthy subjects.[13,18] This agrees with the recent findings on heart failure patients, in whom reduced α was related to mortality.[18]

TABLE II RR Interval Measurements

	VF Group (n = 10)	MI Controls (n = 20)
Traditional measurements		
Time-domain		
Mean RR interval (ms)	879 ± 187	941 ± 133
SDNN (ms)	77 ± 47	98 ± 25
SDANN (ms)	73 ± 34	70 ± 19
Frequency-domain		
ln HF power (ms^2)	6.2 ± 1.5*	5.2 ± 0.9
ln LF power (ms^2)	6.0 ± 1.5	5.8 ± 0.8
ln VLF power (ms^2)	6.9 ± 1.5	7.4 ± 0.7
LF/HF	0.7 ± 0.6†	1.7 ± 1.0
Dynamic measurements		
Fractal-related scaling exponents		
α	0.68 ± 0.18‡	1.11 ± 0.16
β	−1.63 ± 0.24†	−1.33 ± 0.23

*p <0.05; †p <0.01; ‡p <0.001, significance levels for differences between ventricular fibrillation patients and their postinfarction controls. α = short-term fractal-like scaling exponent; β = slope of power-law regression line (from 10^{-4} to 10^{-2} Hz); HF = high-frequency power component of HR variability; LF = low-frequency power component of HR variability; ln = logarithm to the natural base of the absolute value; Mean RR = average of lengths of RR intervals; SDNN = SD of all RR intervals during the 24-hour recording; SDANN = SD of RR intervals of 1 hour before the arrhythmic onset; VLF = very-low-frequency power component of HR variability.

TABLE III RR Interval Measurements of Expanded Groups

	VF Group (n = 15)	MI Controls (n = 30)
Traditional measurements		
Time-domain		
Mean RR interval (ms)	845 ± 200*	980 ± 144
SDNN (ms)	88 ± 49	108 ± 30
SDANN (ms)	72 ± 34	78 ± 28
Frequency-domain		
ln HF power, $msec^2$	6.3 ± 1.6*	5.3 ± 0.9
ln LF power, $msec^2$	5.9 ± 1.6	6.0 ± 0.9
ln VLF power, $msec^2$	6.9 ± 1.4	7.6 ± 0.7
LF/HF	0.9 ± 0.8†	1.9 ± 1.0
Dynamic measurements		
Fractal-related scaling exponents		
α	0.64 ± 0.19‡	1.05 ± 0.12
β	−1.63 ± 0.28‡	−1.31 ± 0.20

Footnotes and abbreviations as in Table II.

Apart from the altered beat to beat dynamics, the long-range correlation properties of RR intervals were also altered before the onset of VF. The computed slope of the power-law relation of HR variability was more negative in patients with VF, despite the absence of differences in the low-frequency spectral components between the groups. The slope of the power-law relation of HR variability computed over ultra- and very-low-frequency oscillations differs from the conventional frequency-domain measurements, because it does not reflect the magnitude of HR variability, but the distribution of spectral characteristics of RR interval oscillations, whereas the traditional spectral measurements calculate the area of the desired spectral band. A steeper (i.e., more negative) slope of the power-law relation has also shown an association with increased mortality in postinfarction patients.[24]

Possible pathophysiologic mechanisms of abnormal short-term dynamics and the propensity for VF: It has been suggested that 1/f signal properties might be an organizing principle of physiologic structure or function. Changes in such organization patterns may result in a less adaptable system favoring vulnerability to various pathologic states.[26,27] We observed that a breakdown of 1/f signal properties, both in short- and in long-term RR interval behavior, precedes the onset of VF, suggesting a possible causal relation between altered fractal-like signal behavior and the onset of life-threatening arrhythmia. However, because the deviations of the short-term slopes from the 1/f curve did not occur immediately before the onset of VF, altered RR interval dynamics may not be a direct trigger of the onset of VF, but may rather reflect changes in other regulatory systems preconditioning the heart to VF.

A potential explanation for the altered correlation properties of HR dynamics preceding VF could be neurohumoral activation (e.g., sympathoexcitation). This theory is supported by observations of the more random RR interval dynamics in heart failure patients[28,29] with high norepinephrine levels.[28] Similar types of HR behavior with abrupt changes in RR intervals have also been observed during intravenous infusion of physiologic doses of norepinephrine in young, healthy adults.[30]

Acknowledgment: The authors appreciate the generous help from Heart Signal Co., Oulu, Finland, and wish to thank Pirkko Huikuri, RN, and Päivi Karjalainen, RN, for technical assistance.

1. Kleiger RE, Stein PK, Bosner MS, Rottman JN. Time domain measurement of heart rate variability. *Cardiol Clin* 1992;10:487–498.
2. Malik M, Camm AJ. Heart rate variability and clinical cardiology. *Br Heart J* 1994;71:3–6.
3. Farrell TG, Bashir Y, Cripps T, Malik M, Poloniecki J, Bennett ED, Ward DE, Camm AJ:Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;18:687–697.
4. Bigger JT Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164–171.
5. Huikuri HV, Koistinen JM, Yli-Mäyry S, Airaksinen KEJ, Seppänen T, Ikäheimo MJ, Myerburg RJ. Impaired low-frequency oscillations of heart rate in patients with prior acute myocardial infarction and life-threatening arrhythmias. *Am J Cardiol* 1995;76:56–60.
6. Vybiral T, Glaeser DH, Goldberger AL, Rigney DR, Hess KR, Mietus J, Skinner JE, Francis M, Pratt CM. Conventional heart rate variability analysis of ambulatory electrocardiographic recordings fails to predict imminent ventricular fibrillation. *J Am Coll Cardiol* 1993;22:557–565.
7. Kimura S, Bassett AL, Kohya T, Kozlovskis PL, Myerburg RJ. Simultaneous recording of action potentials from endocardium and epicardium during ischemia in the isolated cat ventricle: relation of temporal electrophysiologic heterogeneities to arrhythmias. *Circulation* 1986;74:401–409.
8. Lindsay BD, Ambos HD, Schechtman NB, Arthur RM, Cain ME. Noninvasive detection of patients with ischemic and nonischemic heart disease prone to ventricular fibrillation. *J Am Coll Cardiol* 1990;16:1656–1664.
9. Pincus SM, Goldberger AL. Physiologic time-series analysis: what does regularity quantify? *Am J Physiol* 1994;226:H1643–H1656.
10. Denton TA, Diamond GA, Helfant RH, Khan S, Karagueuzian H. Fascinating rhythm: a primer on chaos theory and its applications to cardiology. *Am Heart J* 1990;120:1419–1439.
11. Mayer-Kress G, Yates FE, Benton L, Keidel M, Tirsch W, Pöppl SJ, Geist K. dimensional analysis of nonlinear oscillations in brain, heart, and muscle. *Math Biosci* 1988;90:155–182.
12. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *CHAOS* 1995;1:82–87.
13. Iyengar N, Peng CK, Ladin Z, Wei JY, Goldberger AL, Lipsitz LA. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *Am J Physiol* 1996;271:R1078–R1084.
14. Yamamoto Y, Hughson RL. Coarse-graining spectral analysis:new method for studying heart rate variability. *J Appl Physiol* 1991;71:1143–1150.
15. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci USA* 1991;88:2297–2301.
16. Skinner JE, Pratt CM, Vybiral T. A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular arrhythmias. *Am Heart J* 1993; 125:731–743.
17. Skinner JE, Carpeggiani C, Landisman CE, Fulton KW. Correlation dimension of heartbeat intervals is reduced in conscious pigs by myocardial ischemia. *Circulation Res* 1991;68:966–976.
18. Ho KKL, Moody GB, Peng CK, Mietus JE, Larson MG, Levy D, Goldberger AL. Predicting survival in heart failure cases and controls using fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. *Circulation* 1997;96:842–848.
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 prior myocardial infarction. *J Am Coll Cardiol* 1996;28:1005–1011.
20. Mäkikallio TH, Seppänen T, Airaksinen KEJ, Koistinen J, Tulppo MP, 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.
21. Huikuri HV, Cox M, Interian A, Glicksman F, Kessler KM, Castellanos A, Myerburg RJ. Efficacy of intravenous propranolol for suppression of inducibility of ventricular tachyarrhythmias with different electrophysiologic characteristics in coronary artery disease. *Am J Cardiol* 1989;64:1305–1309.
22. Huikuri HV, Valkama JO, Airaksinen KEJ, Seppänen T, Kessler KM, Takkunen JT, Myerburg RJ. Frequency domain measures of heart rate variability before onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. *Circulation* 1993;87:1220–1228.
23. Kay SM, Marple SL Jr. Spectrum analysis—a modern perspective. *Proc IEEE* 1981;69:1380–1419.
24. 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.
25. Saul JP, Albrecht P, Berger RD, Cohen RJ. Analysis of long-term heart rate variability:methods, 1/f scaling and implications. In: Computers in Cardiology. Silver Spring. MD: IEEE Computer Society Press;1987:419–422.
26. Goldberger AL, West BJ. Applications of nonlinear dynamics to clinical cardiology. *Ann Ny Acad Sci* 1987;504:195–212.
27. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet* 1996;347:1312–1314.
28. Woo MA, Stevenson WG, Moser DK, Middlekauff HR. Complex heart rate variability and serum norepinephrine levels in patients with advanced heart failure. *J Am Coll Cardiol* 1994;23:565–569.
29. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ Haaksma J, Dijk WA, Visser KR, Boomsma F, Dunselman PH. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. *J Am Coll Cardiol* 1996;28:1183–1189.
30. Tulppo MP, Mäkikallio TH, Seppänen T, Airaksinen KEJ, Huikuri HV. Heart rate dynamics during accentuated sympatho-vagal interaction. *Am J Physiol* 1998;274:H810–H816.