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Prediction of Sudden Cardiac Death by Fractal Analysis of Heart Rate Variability in Elderly Subjects

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OBJECTIVES The aim of this study was to test the hypothesis that abnormal scaling characteristics of heart rate (HR) predict sudden cardiac death in a random population of elderly subjects.

BACKGROUND An abnormality in the short-term fractal scaling properties of HR has been observed to be related to a risk of life-threatening arrhythmias among patients with advanced heart diseases. The predictive power of altered short-term scaling properties of HR in general populations is unknown.

METHODS A random sample of 325 subjects, age 65 years or older, who had a comprehensive risk profiling from clinical evaluation, laboratory tests and 24-h Holter recordings were followed up for 10 years. Heart rate dynamics, including conventional and fractal scaling measures of HR variability, were analyzed.

RESULTS At 10 years of follow-up, 164 subjects had died. Seventy-one subjects had died of a cardiac cause, and 29 deaths were defined as sudden cardiac deaths. By univariate analysis, a reduced short-term fractal scaling exponent predicted the occurrence of cardiac death (relative risk [RR] 2.5, 95% confidence interval [CI], 1.9 to 3.2, $p < 0.001$) and provided even stronger prediction of sudden cardiac death (RR 4.1, 95% CI, 2.5 to 6.6, $p < 0.001$). After adjusting for other predictive variables in a multivariate analysis, reduced exponent value remained as an independent predictor of sudden cardiac death (RR 4.3, 95% CI, 2.0 to 9.2, $p < 0.001$).

CONCLUSIONS Altered short-term fractal scaling properties of HR indicate an increased risk for cardiac mortality, particularly sudden cardiac death, in the random population of elderly subjects. (J Am Coll Cardiol 2001;37:1395–402) © 2001 by the American College of Cardiology

Despite the recognition that sudden cardiac arrest accounts for one-half of all coronary heart disease-related deaths and presents as the first manifest of the disease in about 20% to 30% of the deaths, there is little information on specific risk markers of arrhythmic death among the general population (1). Since a large majority of sudden cardiac deaths occur among more general segments of the population, impart as the problem will require sensitive and specific screening methods applicable to the general population. However, the majority of the studies on risk markers of arrhythmic events have focused on the patients with a specific heart disease, often advanced. Large epidemiological surveys have not been able to identify risk markers of sudden death as a specific entity even though general risk markers for atherosclerosis do identify risk of sudden death nonspecifically (2–5).

Measurement of heart rate (HR) variability has provided information on the risk for future arrhythmic events among patients with heart disease. Previous studies in general populations have also shown that abnormal HR variability predicts both nonsudden fatal and nonfatal cardiac events, as well as noncardiac causes of death (6–9). Increasing evidence shows that scaling properties of HR behavior, analyzed by methods based on nonlinear system theory, may provide more powerful information on the risk for life-threatening arrhythmic events than do the traditional measures in the patients with depressed left ventricular function (10–15). In this study, we tested the hypothesis that altered short-term fractal scaling properties of HR predict sudden cardiac death in a randomly selected general population of elderly subjects.

METHODS

Population. In connection with a large survey of the health status of the elderly in the city of Turku, Finland, a random sample of 480 people, age 65 or older, living in the community was obtained from the register of the Social Insurance Institution. The final population comprised 347 subjects, a participation rate of 72%. The final analyses of ambulatory electrocardiographic recordings were available in 325 subjects. Information concerning enrollment, diagnosis, measurement of baseline variables and follow-up has been described in detail previously (16,17). Mortality statistics, hospital records, autopsy findings and death certificates were used to determine the mode of death and mortality after the 10-year follow-up for each subject. Deaths were classified as sudden cardiac, nonsudden car-

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Abbreviations and Acronyms
CI = confidence interval
HR = heart rate
RR = relative risk

diac, cerebrovascular and other causes. A death was determined sudden cardiac death when it occurred within 1 h after the onset of an abrupt change in symptoms and when autopsy data (when available) did not reveal a noncardiac cause of sudden death. Classification of deaths was performed blindly by the events committee before the analysis of HR variability.

HR variability analysis. Twenty-four hour electrocardiographic recordings were performed with a portable two-channel tape recorder (Oxford Medilog, Oxford, United Kingdom). The data were sampled digitally (frequency, 256 Hz) and transferred to a computer for analysis of HR variability. All recordings were first edited automatically followed by careful detailed manual editing. The standard deviation of all normal beat intervals and mean length of the R-R intervals were used for conventional time domain measurements (18).

For long-term scaling analysis, the power-law relationship of R-R intervals was calculated from the frequency range of 10^{-4} to 10^{-2} Hz. The point power spectrum was logarithmically smoothed in the frequency domain, and the power was integrated into bins spaced 0.0167 log (Hz) apart. A robust line-fitting algorithm of log (power) versus log (frequency) was then applied, and the slope of this line was calculated (19), yielding the long-term scaling exponent (β).

For short-term scaling analysis, the detrended fluctuation analysis was used. The method quantifies the fractal-like correlation properties. In this method, the root-mean-square fluctuation of integrated and detrended time series is measured in each observation window and plotted against the size of the window on a log-log scale. Heart rate correlations were defined specifically for short-term (<11 beats, α_1) fluctuation in the data based on the previously established "crossover point" on the log-log plot (11–15,20). Low exponent value near 0.5 corresponds to random dynamics and value near 1.5 to highly correlated interbeat dynamics. The characteristics of fractal analysis by the detrended fluctuation analysis are described in the Appendix. The details of this method have been described previously (20).

Statistical analysis. The baseline data were used as the explanatory variables. The chi-square test was used for categorical and *t* test for continuous variables. A p value <0.05 was considered significant.

Cox proportional hazards regression analyses were used to assess the association between risk predictors and the modes of mortality using SPSS for Windows version 9.0. To find the best cut-off points for HR variability indexes, the dichotomization cut-off points that maximized the hazard ratios were sought, with all-cause mortality as the end point. Kaplan-Meier survival curves with log-rank analysis were computed. Each measure was tested univariately and retested after adjustment for other risk factors. Receiver operating characteristic curves showing sensitivity as functions of the specificity were computed with GraphROC software (Turku, Finland) (21) for comparisons of the performance of HR variability indexes.

RESULTS

After a minimum of 10 years of follow-up, 164 (n = 50.5%) subjects had died. Seventy-one had died of cardiac cause of whom 29 had died suddenly. Among 19 victims who had postmortem examinations, the classification of sudden cardiac death was not contradicted by the presence of diagnosis of cause of death and by the presence of heart disease. Twenty-five additional subjects had died of cerebrovascular disease. Sixty-eight had died due to various other causes, such as cancer, accidents or unknown causes.

Univariate predictors of mortality. Table 1 depicts the values of HR variability indexes in different modes of death and among survivors. Comparisons between the survivors

Table 1. Heart Rate Variability Measures of Survivors, of Subjects Who Died During the Follow-up and of Subjects in Various Mortality Subgroups

	Short-Term Fractal Exponent (α1)	Power-Law Slope (β)	SDNN
Survivors (n = 161, 49.5%)	1.14 ± 0.17	−1.35 ± 0.17	139 ± 35
All-cause mortality (n = 164, 50.5%)	1.03 ± 0.20‡	−1.45 ± 0.21‡	129 ± 36*
Cardiac mortality (n = 71, 43.3% of deaths)	0.97 ± 0.19‡	−1.45 ± 0.20‡	126 ± 35†
Sudden cardiac death (n = 29, 40.8% of cardiac deaths)	0.92 ± 0.19‡	−1.47 ± 0.18‡	123 ± 41*
Autopsy verified sudden cardiac death (n = 19, 26.8% of cardiac deaths)	0.92 ± 0.17‡	−1.49 ± 0.20†	125 ± 43
Nonsudden cardiac mortality (n = 42, 59.2% of cardiac deaths)	1.01 ± 0.19†	−1.44 ± 0.21†	127 ± 32*
Cerebrovascular mortality (n = 25, 15.2% of deaths)	1.08 ± 0.18	−1.49 ± 0.22†	131 ± 37
Noncardiovascular mortality (n = 68, 41.5% of deaths)	1.07 ± 0.22*	−1.41 ± 0.23*	132 ± 38

*p < 0.05; †p < 0.01; ‡p < 0.001 are significance levels for differences. p values determined in Student *t* test analysis.
SDNN = standard deviation of all N-N intervals.

Table 2. Unadjusted and Adjusted Association of Heart Rate Variability Variables With All-Cause Mortality, Cardiac Mortality, Sudden Cardiac Mortality, Sudden Cardiac Autopsy-Verified Mortality, Sudden Cardiac Mortality for Both Genders, Nonsudden Cardiac Mortality and Nonsudden Cardiac Mortality With Cerebrovascular Mortality

	Unadjusted Association			Association Adjusted for All Risk Variables		
	Relative Risk	95% CI	p Value	Relative Risk	95% CI	p Value
All-cause mortality						
Short-term fractal exponent ($\alpha_1 < 1.0$)	1.7	(1.4–1.9)	< 0.001	1.4	(1.1–1.7)	< 0.01
SDNN (<120 ms)	1.3	(1.1–1.6)	< 0.01	1.1	(0.9–1.3)	NS
Power-law ($\beta < -1.5$)	1.8	(1.4–1.9)	< 0.001	1.6	(1.3–1.9)	< 0.001
Cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	2.5	(1.9–3.2)	< 0.001	2.1	(1.5–2.9)	< 0.001
SDNN (<120 ms)	1.4	(1.1–1.8)	< 0.05	0.9	(0.6–1.2)	NS
Power-law ($\beta < -1.5$)	2.3	(1.7–3.1)	< 0.001	1.7	(1.3–2.5)	< 0.001
Sudden cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	4.1	(2.5–6.6)	< 0.001	4.3	(2.0–9.2)	< 0.001
SDNN (<120 ms)	1.6	(1.1–2.4)	< 0.05	1.1	(0.6–2.1)	NS
Power-law ($\beta < -1.5$)	2.2	(1.5–3.1)	< 0.001	1.9	(0.9–4.0)	NS
Autopsy-verified sudden cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	4.5	(2.4–8.4)	< 0.001	4.9	(1.8–13.4)	< 0.01
SDNN (<120 ms)	1.6	(0.9–2.7)	NS	1.3	(0.5–3.2)	NS
Power-law ($\beta < -1.5$)	2.8	(1.7–4.4)	< 0.001	2.8	(1.2–6.7)	< 0.05
Sudden cardiac death in men						
Short-term fractal exponent ($\alpha_1 < 1.0$)	5.9	(2.8–12.5)	< 0.001	5.3	(1.4–20.8)	< 0.05
SDNN (<120 ms)	2.2	(1.2–4.1)	< 0.01	1.0	(0.3–3.2)	NS
Power-law ($\beta < -1.5$)	2.0	(1.2–3.5)	< 0.05	2.2	(0.6–8.1)	NS
Sudden cardiac death in women						
Short-term fractal exponent ($\alpha_1 < 1.0$)	3.1	(1.7–5.8)	< 0.001	2.4	(1.0–5.9)	< 0.05
SDNN (<120 ms)	1.2	(0.6–2.2)	NS	0.7	(0.2–2.0)	NS
Power-law ($\beta < -1.5$)	2.5	(1.5–4.3)	< 0.001	1.6	(0.7–4.0)	NS
Nonsudden cardiac death						
Short-term fractal exponent ($\alpha_1 < 1.0$)	2.2	(1.6–3.0)	< 0.001	1.7	(1.1–2.8)	< 0.05
SDNN (<120 ms)	1.4	(1.0–1.9)	< 0.05	0.8	(0.5–1.3)	NS
Power-law ($\beta < -1.5$)	2.3	(1.7–3.4)	< 0.001	1.7	(1.1–2.5)	< 0.05
Cerebrovascular mortality						
Short-term fractal exponent ($\alpha_1 < 1.0$)	1.5	(0.9–2.4)	NS	1.2	(0.7–2.2)	NS
SDNN (<120 ms)	1.7	(1.1–2.4)	< 0.05	1.6	(1.0–2.5)	NS
Power-law ($\beta < -1.5$)	2.0	(1.4–3.0)	< 0.001	2.8	(1.7–4.8)	< 0.001
Noncardiovascular mortality						
Short-term fractal exponent ($\alpha_1 < 1.0$)	1.4	(1.1–1.9)	< 0.01	1.1	(0.8–1.5)	NS
SDNN (<120 ms)	1.2	(0.9–1.6)	NS	1.1	(0.9–1.6)	NS
Power-law ($\beta < -1.5$)	1.8	(1.3–2.5)	< 0.001	1.6	(1.2–2.5)	< 0.001

p values determined in univariate and multivariate Cox regression analysis.
α = short-term fractal exponent; β = power-law slope of RR intervals; CI = confidence intervals; SDNN = standard deviation of all N-N intervals.

and those who had died identified the short-term fractal scaling exponent (α_1) as having an association with overall mortality (relative risk [RR] 1.7, 95% confidence interval [CI], 1.4 to 1.9, $p < 0.001$). The reduced exponent value (<1.0) was the dichotomized variable that robustly predicted cardiac death (RR 2.5, 95% CI, 1.9 to 3.2, $p < 0.001$). It was an even stronger predictor of sudden cardiac death (RR 4.1, 95% CI, 2.5 to 6.6, $p < 0.001$), in particular among men (RR 5.9, 95% CI, 2.8 to 12.5, $p < 0.001$). Results were similar among the subjects with autopsy-documented sudden cardiac death (Table 2). Short-term exponent also predicted nonsudden cardiac mortality but not cerebrovascular mortality (Table 2).

Baseline characteristics of survivors and subjects who had died have been reported in details previously (9). The clinical variables associated with overall mortality in univariate analyses were age, gender, history of congestive heart failure, angina pectoris, prior myocardial infarction or history of cerebrovascular disease, functional class, use of cardiac medication, smoking as well as lipid and glucose values. Among all analyzed variables, the short-term scaling exponent was the most powerful predictor of cardiac mortality and a particularly strong predictor of sudden cardiac death. Figure 1 shows Kaplan-Meier survival curves and different modes of mortality predicted by the exponent.

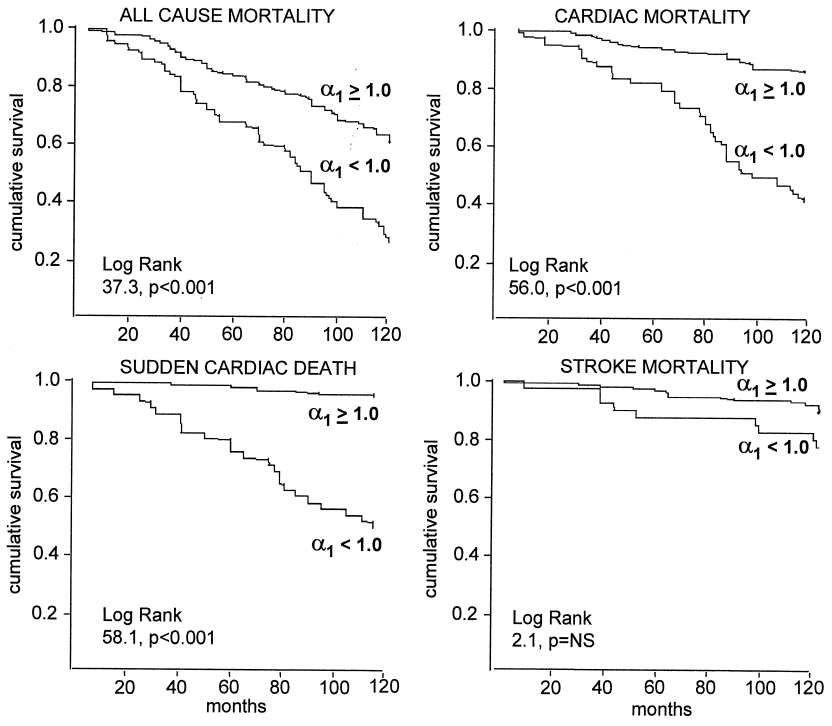

Figure 1. Kaplan-Meier survival curves for the all-cause mortality, cardiac mortality, sudden cardiac deaths, as well as cerebrovascular mortality with the short-term fractal exponent of heart rate dynamics <1.0 or ≥1.0. Short-term fractal exponent was a particularly powerful predictor of sudden cardiac death with very high negative predictive accuracy **(upper panel, right)**. Short-term fractal exponent did not predict cerebrovascular mortality as seen in the **lower right panel**.

Associations between short-term exponent and other risk factors. The short-term exponent showed a weak negative correlation with age ($r = -0.19$, $p < 0.001$). Table 3 shows the association of dichotomized exponent value with various demographic and clinical risk variables. A reduced exponent was more often observed in subjects with a history of heart failure, angina pectoris, previous myocardial infarction, functional class III or IV and in those who used cardiac medication. It was also weakly associated with the frequency of premature ventricular beats (Table 3).

Multivariate predictors of mortality. Table 2 shows the multivariate relative risks for HR variability measures adjusted for other risk variables, such as age, gender, heart failure, angina pectoris, functional class, previous myocardial infarction, cardiac medication and ventricular premature beats. Although the short-term exponent had weak associations to various clinical parameters (Table 3), it remained as a strong independent predictor of sudden cardiac death after adjustment for other variables in multivariate analysis. Long-term power-law exponent also independently predicted cardiac and cerebrovascular mortality, but the standard deviation of R-R intervals had no independent prognostic power after adjustment for other risk factors.

A subgroup analysis was performed for subjects without known or suspected heart disease at the time of entry by excluding subjects with angina pectoris, previous myocardial infarction, heart failure, impaired functional class and subjects taking any cardiac medication. Among this apparently healthy subgroup ($n = 167$), short-term exponent also provided significant unadjusted and adjusted prognostic power for predicting cardiac mortality (RR 4.0, 95% CI 1.9 to 8.9, $p < 0.001$ and RR 6.7, 95% CI 1.7 to 25.5, $p < 0.001$, respectively). Although only four cases of sudden cardiac death occurred in this subgroup, a number too small to analyze, they all had an exponent value <1.0.

Accuracy of HR variability predictors of mortality. Among different R-R interval variability measures, the reduced short-term exponent had the best sensitivity in all specificity levels in predicting cardiac mortality and sudden cardiac death. The area under the curve representing discrimination with short-term fractal exponent was significantly higher than are area under the curve of standard deviation of R-R intervals in predicting cardiac mortality and sudden cardiac death ($p < 0.05$ for both) (Fig. 2).

DISCUSSION

The main finding of this study is that altered short-term fractal scaling exponent of HR dynamics is a powerful predictor of cardiac death and, particularly, of sudden cardiac death in an unselected elderly population. All other HR variability measures were surpassed by this variable in the prediction of cardiac mortality.

Prognostic power of HR variability in general population. Previous studies have shown that altered long-term variability measurements predict mortality both in the

Table 3. The Number of Subjects With Short-Term Fractal Cut-Off Point Value <1 and ≥1 in Different Mortality and Clinical Variable Categories

	Exponent $\alpha_1 < 1$ (n = 107)	Exponent $\alpha_1 \geq 1$ (n = 218)	p Value
Mortality Categories			
Survivors (n = 161)	27 (25.2%)	134 (61.5%)	
All-cause mortality (n = 164)	80 (74.8%)	84 (38.5%)	‡
Cardiac mortality (n = 71)	48 (44.9%)	23 (10.6%)	‡
Sudden cardiac death (n = 29)	24 (22.4%)	5 (2.3%)	‡
Nonsudden cardiac mortality (n = 42)	24 (22.4%)	18 (8.3%)	‡
Cerebrovascular mortality (n = 25)	9 (8.4%)	16 (7.3%)	
Noncardiovascular mortality (n = 68)	23 (21.5%)	45 (20.6%)	†
Clinical Variables			
Age: ≤75 yrs (n = 216)	62 (57.9%)	154 (70.6%)	
Age: >75 yrs (n = 109)	45 (42.1%)	64 (29.4%)	†
Men (n = 173)	52 (48.6%)	121 (55.5%)	
Women (n = 152)	55 (51.4%)	97 (44.5%)	
Current or ex-smoker (n = 145)	51 (47.7%)	94 (43.1%)	
Diabetes (n = 35)	12 (11.2%)	23 (10.6%)	
Hypertension (n = 48)	20 (18.7%)	28 (12.8%)	
Heart failure (n = 35)	20 (18.7%)	15 (6.9%)	‡
Angina pectoris (n = 56)	25 (23.4%)	31 (14.2%)	*
PVCs > 10/h (n = 47)	22 (20.6%)	25 (11.5%)	*
NYHA class III–IV (n = 85)	44 (41.1%)	41 (18.8%)	‡
Prior MI (n = 23)	12 (11.2%)	11 (5.0%)	*
Cardiac medication (n = 95)	46 (43.0%)	49 (22.5%)	‡
Subjects free of AP, CHF, prior MI, NYHA III–IV class and cardiac medication	41 (38.3%)	126 (57.8%)	‡

*p < 0.05; †p < 0.01; ‡p < 0.001 are significance levels for differences.
AP = angina pectoris; α_1 = short-term fractal exponent; CHF = congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association; PVC = premature ventricular complex.

patients with documented heart disease, as well as in random general populations (6–9). In addition to being a marker of cardiac mortality, reduced variability has been associated with various noncardiac causes of death (6,9). In this study, altered short-term fluctuations were found to yield more powerful prognostic information on the risk of cardiac death than any long-term index or clinical variable. Unlike the long-term HR variability indexes, it failed to predict cerebrovascular death. This suggests that altered short-term dynamics of HR may specifically reflect abnormalities in cardiac neural regulation, but reduction in overall long-term variability seems to be related to an increased risk for various other events and progression of atherosclerosis (6–9,22,23).

Association of short-term fractal scaling exponent to life-threatening arrhythmia. The finding that the short-term scaling exponent predicted sudden cardiac death specifically is in accordance with studies that included patients

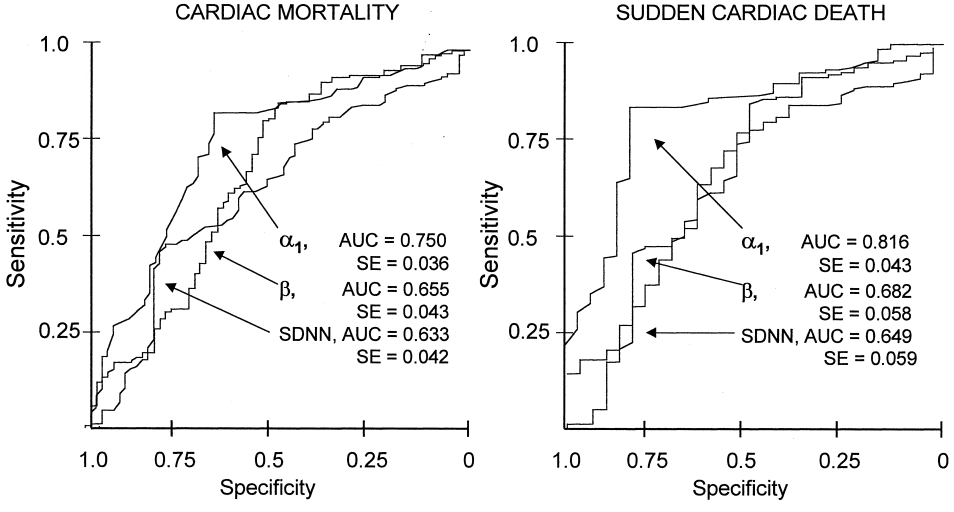

Figure 2. Receiver operating characteristic curves for the short-term fractal exponent, long-term scaling exponent and for SDNN in predicting cardiac death and sudden cardiac death. Short-term fractal exponent had higher sensitivity than SDNN or long-term scaling exponent in all specificity levels. AUC = area under the curve; SDNN = standard deviation of all N-N intervals.

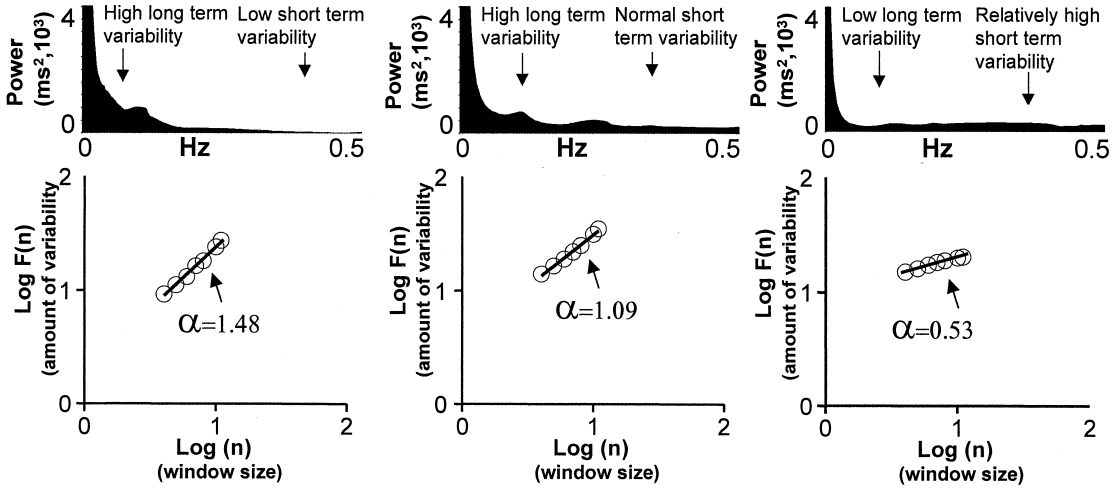

Figure 3. Examples of power spectra and different fractal scaling exponent values. High exponent values are seen when predominant low frequency fluctuation is present and high frequency fluctuation is reduced **(left panel)**. Low exponent values are seen in cases with reduced low and very low frequency fluctuations and either reduced or preserved high frequency fluctuations **(right panel)**. "Normal" fractal scaling value near 1.0 is seen when both low and high frequency power are relatively preserved with more power in the very low and low frequency areas than in the high frequency area **(middle panel)**.

with a prior myocardial infarction and have documented an association with altered short-term exponent and life-threatening arrhythmias (11,12). In addition, it has also been shown to provide powerful prognostic information on the risk of death among the patients with depressed left ventricular function (13,14). These findings generalize the application of short-term scaling exponent as a risk stratifier of sudden cardiac death beyond the patient populations considered at increased risk of fatal arrhythmias (10–15) to the general elderly population. The accuracy of the short-term fractal exponent as a single risk marker in sudden cardiac death prediction outweighed the general risk markers of cardiac death. It performed better as a predictor of sudden cardiac death among the men than it did among the women, which may be partially explained by a recent study showing gender difference in scaling exponents (24).

Possible mechanisms of altered short-term fractal properties of HR as a risk factor for cardiac mortality. Normal values of traditional HR variability indexes vary interindividually to a great extent. However, fractal indexes have quite a small interindividual variation in their normal values, so that short-term exponent values below 1.0 are rarely seen among healthy middle-aged subjects (11,24). Even small alterations from this normal "fractal-like" HR dynamic seem to reflect specific perturbation in the cardiovascular regulation system, leading to a higher cardiac mortality rate. The value of 1.0 turned out to be the best discriminator of mortality in this general elderly population. Notably, this particular exponent value corresponding to 1/f noise is a well-characterized physical phenomenon. In this study, subjects with less temporally correlated short-term R-R intervals had the worst prognosis, indicating that the alterations of short-term "memory properties" between interbeat intervals are deleterious.

The physiological background of abnormal fractal correlation properties associated with increased risk of dying for cardiac cause is not clear. However, increasing evidence supports the role of the sympathetic activation behind this impairment. High norepinephrine levels, indicating sympathoexcitation, have been observed to be related to random R-R interval dynamics in heart failure patients (25). Interestingly, in young healthy adults, an intravenous infusion of physiologic doses of norepinephrine has been shown to lead to altered fractality, demonstrated by sudden abrupt changes in short-term HR dynamics (26).

Study limitations. The relatively small study cohort is a limitation of this study. However, only elderly subjects were included, and the uniform 10-year follow-up period, with a larger number of deaths than in previous studies (7,8,27,28), allowed the evaluation of different causes of mortality among a general elderly population. Nonetheless, autopsy data were available in two-thirds of the sudden death cases, reducing the uncertainty regarding the exact mode of death, which can cause end point bias in observational follow-up studies. We also note that we selected only one time domain index of HR variability and fractal scaling indexes for this study. However, we also analyzed the data using frequency domain indexes (18) and complexity measures of approximate entropy (29,30). The former showed a weaker prognostic power than the fractal scaling measures, and the latter showed no prognostic power (data not presented).

Conclusions. The data of this observational study in a random elderly cohort suggest that analysis of short-term behavior of HR dynamics provide a specific risk marker of cardiac death, particularly sudden cardiac death. If these data are confirmed in other larger prospective studies, analysis of scaling features of short-term HR dynamics may become a useful clinical tool for risk stratification.

APPENDIX

DFA analysis. Details of detrended fluctuation analysis have been described previously elsewhere (20). Briefly, scaling exponent obtained by detrended fluctuation analysis quantifies the relations of heart rate (HR) fluctuations at different scales. Low exponent values correspond to dynamics where magnitude of beat-to-beat HR variability is close to magnitude of longer-term variability. On the contrary, high exponent values correspond to dynamics where the magnitude of long-term variability is substantially higher than beat-to-beat variability. Different scaling exponent values can also be understood via spectral properties of data. Exponent values correlate with normalized spectral measures in controlled situations, and, for example, low to high frequency spectral ratio is closely related to the short-term fractal scaling exponent in controlled external situations with fixed respiratory rate. However, this is not the case during "free-running" ambulatory conditions (31) because fractal analysis by the DFA technique provides precise information on the scaling properties of HR fluctuations over highly segmented time windows, while conventionally computed spectral measures vaguely describe HR fluctuations in predetermined time windows. Thus, fractal analysis can be considered to be a modification of spectral analysis, but, unlike the spectral analysis, it is not polluted by changes in the external environment, such as respiration and physical activity. Therefore, fractal scaling exponents are not surrogates of spectral components when analyzed from the ambulatory Holter recordings. Figure 3 describes examples of power spectra in cases with various scaling exponent values.

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REFERENCES

1. Myerburg RJ, Interian A, Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 1997;80:10F–9F.
2. Kannel WB, Cupples LA, D'Agostino RB. Sudden death risk in overt coronary heart disease: the Framingham study. Am Heart J 1987;113: 799–804.
3. Kreger BE, Cupples LA, Kannel WB. The electrocardiogram in prediction of sudden death: Framingham study experience. Am Heart J 1987;113:377–82.
4. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham heart study experience). Am J Cardiol 1991;67:55–8.
5. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham study. JAMA 1987;257: 2176–82.
6. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: the Zutphen study. Am J Epidemiol 1997;145:899–908.
7. Tsuji H, Vendetti FJ, Jr, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort: the Framingham heart study. Circulation 1994;90:878–83.
8. Tsuji H, Larson MG, Vendetti FJ, Jr, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham heart study. Circulation 1996;94:2850–5.
9. Huikuri HV, Mäkikallio TH, Airaksinen KEJ, et al. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. Circulation 1998;97:2031–6.
10. Skinner JE, Pratt CM, Vybiral T. A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. Am Heart J 1993;125:731–43.
11. Mäkikallio TH, Seppänen T, Airaksinen KEJ, et al. Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. Am J Cardiol 1997;80:779–83.
12. Mäkikallio TH, Koistinen MJ, Jordaens L, et al. Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts. Am J Cardiol 1999;83:880–4.
13. Mäkikallio TH, Hoiber S, Kober L, et al. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. Am J Cardiol 1999;83:836–9.
14. Huikuri HV, Mäkikallio TH, Peng CK, Goldberger AL, Hintze U, Møller M. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. Circulation 2000;101:47–53.
15. Ho KKL, Moody GB, Peng CK, et 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;96:842–8.
16. Sourander LB, Saraste M, Konu V, Piha J, Seppänen A, Kallio V. Continuous ambulatory ECG recordings in a random sample of the aged in Turku. J Clin Exp Gerontol 1986;4:315–36.
17. Räihä IJ, Piha SJ, Seppänen A, Puukka P, Sourander LB. Predictive value of continuous ambulatory electrocardiographic monitoring in elderly people. Br Med J 1994;309:1263–7.
18. 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;93:1043–65.
19. Bigger JT, Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrect 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;93:2142–51.
20. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 1995;5:82–7.
21. Kairisto V, Poola A. Sofrware for illustrative presentation of basic clinical characteristics of laboratory tests—GraphROC for Windows. Scand J Clin Lab Invest 1995;55:43–60.
22. Korpelainen JT, Sotaniemi KA, Mäkikallio A, Huikuri HV, Myllylä VV. Dynamic behavior of heart rate in ischemic stroke. Stroke 1999;30:1008–13.
23. Liao D, Cai J, Rosamond WD, et al. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study: the ARIC study (Atherosclerosis Risk In Communities study). Am J Epidemiol 1997;145:696–706.
24. Pikkujämsä SM, Mäkikallio TH, Soudarder LB, et al. Cardiac interbeat interval dynamics from childhood to senescence: comparison of conventional and new measures based on fractals and chaos theory. Circulation 1999;100:393–9.
25. 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;23:565–9.
26. Tulppo MP, Mäkikallio TH, Seppänen T, Airaksinen KEJ, Huikuri HV. Heart rate dynamics during accentuated sympathovagal interaction. Am J Physiol 1998;274:H810–6.
27. LaRovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ, for the ATRAMI Investigators. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 1998;351:478–84.

28. Kleiger RE, Miller JP, Bigger JT, Moss AJ, for the Multicenter Postinfarction Research Group. Decreased heart rate variability and its association with increased mortality after myocardial infarction. Am J Cardiol 1987;59:256–62.
29. Pincus SM. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci USA 1991;88:2297–301.
30. 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;28:1005–11.
31. Tulppo MP, Hughson RL, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Huikuri HV. Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics. Am J Phys. In Press.