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Power-Law Relationship of Heart Rate Variability as a Predictor of Mortality in the Elderly

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Background—The prognostic role of heart rate (HR) variability analyzed from 24-hour ECG recordings in the general population is not well known. We studied whether analysis of 24-hour HR behavior is able to predict mortality in a random population of elderly subjects.

Methods and Results—A random sample of 347 subjects of ≥ 65 years of age (mean, 73 ± 6 years) underwent a comprehensive clinical evaluation, laboratory tests, and 24-hour ECG recordings and were subsequently followed up for 10 years. Various spectral and nonspectral measures of HR variability were analyzed from the baseline 24-hour ECG recordings. Risk factors for all-cause, cardiac, cerebrovascular, cancer, and other causes of death were assessed. By the end of 10-year follow-up, 184 subjects (53%) had died and 163 (47%) were still alive. Seventy-four subjects (21%) had died of cardiac disease, 37 of cancer (11%), 25 of cerebrovascular disease (7%), and 48 (14%) of various other causes. Among all analyzed variables, a steep slope of the power-law regression line of HR variability (< -1.50) was the best univariate predictor of all-cause mortality (odds ratio, 7.9; 95% confidence interval [CI], 3.7 to 17.0; $P < .0001$). After adjusting for age and sex and including all univariate predictors of mortality in the proportional hazards analysis, ie, measures of HR variability, history of heart disease, functional class, smoking, medication, and blood cholesterol and glucose concentrations, all-cause mortality was predicted only by the slope of HR variability (adjusted relative risk, 1.74; 95% CI, 1.42 to 2.13; $P < .0001$) and a history of congestive heart failure (adjusted relative risk, 1.70; $P = .0002$). The slope of HR variability predicted both cardiac (adjusted relative risk, 2.05; $P = .0002$) and cerebrovascular death (adjusted relative risk, 2.84; $P = .0001$) but not cancer or other causes of death.

Conclusions—Power-law relationship of 24-hour HR variability is a more powerful predictor of death than the traditional risk markers in elderly subjects. Altered long-term behavior of HR implies an increased risk of vascular causes of death rather than being a marker of any disease or frailty leading to death. (*Circulation*. 1998;97:2031-2036.)

Key Words: population ■ death, sudden ■ intervals ■ aging

Because the prognostic significance of conventional risk factors applicable to younger ages tends to disappear in old age,¹⁻⁴ it is important to find new prognostic and diagnostic markers to define the risk of death and to develop therapeutic strategies to prevent premature death among elderly subjects.

HR variability measurements from 24-hour ambulatory ECG recordings provide prognostic information in patients with heart disease,^{5,6} but their prognostic role is not well established in general populations. In patients with a recent myocardial infarction, analysis of the spectral characteristics of 24-hour HR variability has been observed to yield prognostic information beyond that provided by the traditional short-term measures of HR variability.^{6,7} The purpose of the present investigation was to assess the ability of 24-hour HR variability to predict mortality in a random population of elderly subjects. We also studied whether analysis of the spectral characteristics of long-term HR behavior performs

any better than the traditional measures of HR variability or other common risk markers for predicting various causes of death during long-term follow-up.

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 persons ≥ 65 years of age living in the community was obtained from the register of the Social Insurance Institution.⁸⁻¹⁰ No exclusion criteria other than living in an institution were used. The participation rate of these subjects was 72%; ie, the final series consisted of 347 subjects. Details concerning enrollment, measurement of baseline variables, and follow-up have been described previously.⁸⁻¹⁰ The final analysis of ambulatory ECG recordings included 325 subjects; 22 subjects had to be excluded because of atrial fibrillation ($n = 14$), evidence of sick sinus syndrome ($n = 2$), or technical artifacts ($n = 6$) during the 24-hour ambulatory ECG.

A clinical history was obtained by personal interview, and a comprehensive clinical evaluation was carried out, including classi-

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Selected Abbreviations and Acronyms

HF	= high frequency
HR	= heart rate
LF	= low frequency
SDNN	= standard deviation of all R-R intervals
ULF	= ultra-low frequency
VLF	= very low frequency

fication of functional class, physical examination, standard ECG, chest x-ray, blood pressure, and biochemical analyses.⁸⁻¹⁰ Major diagnoses were established on the basis of the history, clinical evaluation, ECG and chest x-ray findings, and laboratory data.⁸⁻¹⁰ Ischemic heart disease was diagnosed by a standard questionnaire concerning any history of angina pectoris. Myocardial infarction was defined from the clinical history and from Q-wave abnormalities on the ECG, according to the Minnesota code. Additional information for the diagnostic criteria was obtained from the subject's national health insurance documents.^{9,10} Serum total cholesterol, HDL and LDL cholesterol, triglycerides, and glucose were measured from overnight fasting samples by the methods described earlier.¹¹

Ten-year mortality and causes of deaths were recorded from the mortality statistics. The mode of death was defined after a review of the hospital records, autopsy findings, and death certificates. Non-fatal cardiovascular events (acute myocardial infarction, unstable angina pectoris, transient ischemic attacks, and stroke) were retrospectively analyzed from the hospital records according to the corresponding diagnostic codes (ICD 8 and 9 classification). The end points were all-cause mortality, cardiac mortality, cerebrovascular mortality, cancer mortality, mortality from various other causes, and nonfatal cardiovascular events.

Ambulatory ECG Recordings

Twenty-four-hour continuous ambulatory ECG recordings were performed with a portable two-channel tape recorder (Oxford Medilog).^{8,9} The recordings were analyzed with the replay and analysis units described in detail previously.^{8,9} The subjects were encouraged to continue with their normal everyday activities during the recordings. Ventricular arrhythmias were classified as (1) ≥ 10 or < 10 ventricular premature beats per hour and (2) episode(s) of ventricular tachycardia (≥ 3 consecutive beats).

Analysis of HR Variability

The ECG data were sampled digitally and transferred from the Oxford Medilog scanner to a microcomputer for analysis of HR variability. All R-R interval time series were first edited automatically, after which careful manual editing was performed by visual inspection of the R-R intervals. Each R-R interval time series was passed through a filter that eliminates premature beats and artifacts and deletes the filling gaps with previously described methods.^{12,13} Only recordings with qualified beats for at least a 20-hour period and with $> 85\%$ of qualified sinus beats were included in the analysis of HR variability ($n=305$). The average duration of the recordings was 23 hours.

After editing of the R-R interval tachograms, the R-R interval spectrum was computed over the entire recording interval according to a previously described method.¹⁴ A fast Fourier transform method was used to estimate the power spectrum densities of HR variability. Frequency domain measures of R-R interval variability were computed by integrating the point power spectrum over the frequency intervals. The power spectra were quantified by measuring the areas in the following frequency bands (1) < 0.0033 Hz, (ULF power), (2) 0.0033 to < 0.04 Hz (VLF power), (3) 0.04 to 0.15 Hz (LF power), and (4) 0.15 to < 0.40 Hz (HF power). The SDNN was used as a time-domain measure of HR variability. The power-law relationship of R-R interval variability was calculated from the frequency range of 10^{-4} to 10^{-2} by a previously described method.⁷ The point power spectrum was logarithmically smoothed in the frequency domain, and the power was integrated into bins spaced 0.0167 log(Hz) apart.

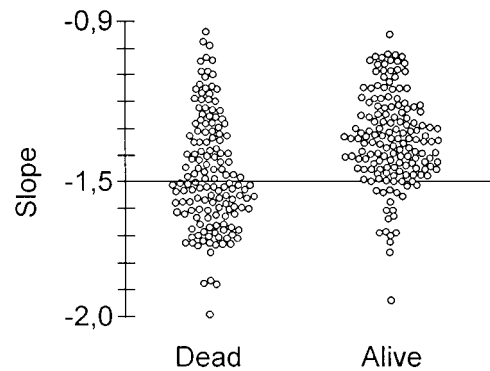


Figure 1. Individual values of the slope of power-law regression line computed over frequencies between 10^{-2} and 10^{-4} for subjects who were alive and for those who died during the 10-year follow-up.

A robust line fitting algorithm of $\log(\text{power})$ on $\log(\text{frequency})$ was then applied to the power spectrum between 10^{-4} and 10^{-2} , and the slope of this line was calculated (see examples in Fig 1). This frequency band was chosen on the basis of previous observations regarding the linear relationship between $\log(\text{power})$ and $\log(\text{frequency})$ in this frequency band.^{7,14}

Statistical Analysis

The data collected at the baseline examination were used as the explanatory variables in univariate comparisons between the subjects who had remained alive throughout the follow-up and those who had died. The frequency-domain measures of HR variability were transformed to natural logarithms because their distributions were skewed. Univariate comparisons of baseline characteristics between the subjects who had died and those who were alive at the end of the follow-up were performed with the χ^2 test for categorical variables and with the two-sample t test for continuous variables. Odds ratios and 95% confidence intervals were also calculated for each univariate predictor of all-cause mortality. A value of $P < .05$ was considered to indicate statistical significance.

Cox proportional hazards regression analyses were used to assess the association between different risk predictors and mortality by use of SPSS for Windows version 6.1. To find the best cutoff points for various measures of HR variability, the dichotomization cutoff points that maximized the hazards ratio obtained from the Cox regression model were sought, with all-cause mortality as the end point. All the proportional hazards regression analyses were stratified with sex and age as covariates. In addition, all the variables that had a univariate association with all-cause mortality ($P < .05$) were included in the model to estimate the independent power of the various variables in predicting the mortality. Kaplan-Meier estimates of the distribution of times from the baseline to death were computed; log-rank analysis was performed to compare the survival curves between the groups.

Results

Univariate Predictors of Mortality

By the end of 10-year follow-up 184 subjects (53%) had died and 167 (47%) were still alive. Seventy-four subjects (21%) had died of cardiac disease, 37 of cancer (11%), 25 of cerebrovascular disease (7%), and 48 (14%) of various other causes. Baseline characteristics of subjects who had died during the follow-up and those who were still alive are shown in Table 1. Univariate comparison showed age, sex, history of congestive heart failure, angina pectoris, prior myocardial infarction or cerebrovascular disease, functional class, use of cardiac medication, and smoking history to be associated with

TABLE 1. Baseline Characteristics of the Subjects Who Had Died by the End of the 10-Year Follow-up and Those Who Had Remained Alive

	Alive (n=163)	Dead (n=184)	P*
Clinical and laboratory data			
Age, y	71±5	76±6	<.001
Sex, M/F	70/93	108/76	<.05
Functional class, n (%)			
1	99 (61)	67 (36)	NS
2	43 (26)	47 (26)	NS
3-4	21 (13)	70 (38)	<.001
Smoking, n (%)			
Never smoked	103 (63)	83 (45)	<.01
Ex-smoker	43 (26)	75 (41)	NS
Current smoker	17 (11)	26 (14)	NS
Medical history, n (%)			
Diabetes	16 (10)	22 (13)	NS
Hypertension	36 (22)	23 (14)	NS
CVD	4 (2)	20 (12)	<.01
Prior AMI	4 (2)	25 (15)	<.001
Angina pectoris	16 (10)	41 (25)	<.001
CHF	8 (5)	34 (20)	<.001
Cancer	5 (3)	10 (6)	NS
Cardiac medication	30 (18)	67 (40)	<.001
BMI, kg/m ²	26.9±3.7	25.9±4.0	NS
Systolic blood pressure, mm Hg	158±21	158±19	NS
Diastolic blood pressure, mm Hg	90±11	90±9	NS
Glucose, mmol/L	5.2±1.5	5.8±2.7	<.01
Cholesterol, mmol/L	6.7±1.3	6.3±1.3	<.01
HDL cholesterol, mmol/L	1.44±0.35	1.41±0.41	NS
Triglyceride, mmol/L	1.43±0.58	1.44±0.72	NS
Ambulatory ECG data			
Average R-R-interval, ms	848±121	864±199	NS
SDNN, ms	139±35	129±36	<.01
ULF power, ms ²	13 579±5647	11 174±2338	
ln	9.2±0.52	9.1±0.91	NS
VLF power, ms ²	1012±1065	759±515	
ln	6.7±0.6	6.3±0.8	<.001
LF power, ms ²	598±491	563±462	
ln	5.8±0.7	5.6±1.0	<.05
HF power, ms ²	238±243	332±819	
ln	5.3±0.7	5.3±1.1	NS
Slope of HRV	-1.35±0.17	-1.46±0.21	<.001
VPBs≥10/h	19 (12)	35 (19)	<.05
Episodes of VT	6 (4)	11 (6)	NS

CVD indicates cerebrovascular disease; AMI, acute myocardial infarction; CHF, congestive heart failure; BMI, body mass index; Slope of HRV, slope of regression line of log(power) – log(frequency) of HR variability between frequencies 10⁻² and 10⁻⁴; VPBs, ventricular premature depolarizations; and VT, ventricular tachycardia.

*Calculated with the two-sample *t* test for continuous variables and by the χ^2 test for other variables.

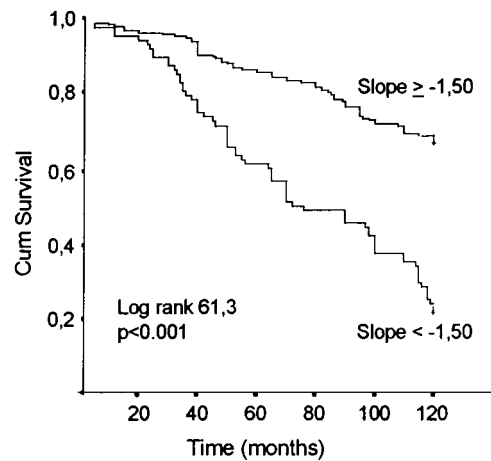


Figure 2. Kaplan-Meier survival curves for the subjects with the slope of the power-law regression line of HR variability <-1.50 or ≥-1.50. Estimated cumulative (Cum) survival rate over a 10-year period was 67% in those with a slope ≥-1.50 and 20% in those with a slope <-1.50.

all-cause mortality. The subjects who subsequently died also had elevated baseline blood glucose and lower cholesterol concentrations relative to those who remained alive during the follow-up.

Comparison of the HR variability measures between the survivors and those who had died pointed to the slope of the power-law regression line of HR variability, SDNN, and the VLF and LF spectral components as having a univariate association with all-cause mortality (Table 1). Because the SDNN and the VLF and LF frequency components of HR variability had close univariate correlations with each other (*r*>.7 for all) but the slope of the power-law regression line had only a weak correlation with SDNN (*r*=.16, *P*<.01), VLF (*r*=.37, *P*<.001), or LF (*r*=.34, *P*<.001), a stepwise proportional hazards method was used to reveal the independent prognostic power of each measure. This showed both the slope of the regression line and SDNN to possess independent predictive power with respect to all-cause mortality (*P*<.001 for both), whereas the VLF and LF power spectral components did not enter the model as independent predictors. The best cutoff points for predicting mortality were <-1.50 for the slope of the power-law regression line (94 subjects, 31%) and <120 ms for SDNN (100 subjects, 33%), and these were used as dichotomized cutoff points in the multivariate analyses.

Among all analyzed clinical, laboratory, and Holter variables, the slope of the power-law regression line was the best univariate predictor of all-cause mortality (odds ratio, 7.9; 95% confidence interval, 3.7 to 17.0; *P*<.0001; Figs 1 and 2). Overall mortality was also high (36 of 42 subjects, 85%) among the subgroup of subjects in whom the heart rate variability could not be analyzed, mostly because of atrial fibrillation or frequent ventricular premature beats during the recording.

Multivariate Predictors of Mortality

Table 2 shows the significances and relative risks attached to various clinical, laboratory, and ambulatory ECG variables

TABLE 2. Significant Predictors of All-Cause Mortality in Proportional Hazards Regression Analysis

	Age- and Sex-Adjusted Association With Mortality			Association With Mortality Adjusted for All Variables		
	Relative Risk	95% CI	P*	Relative Risk	95% CI	P*
Clinical and laboratory variables						
Prior AMI	1.39	1.12–1.74	.003	0.82	0.58–1.14	NS
Angina pectoris	1.40	1.17–1.67	.003	1.23	0.90–1.66	NS
CHF	1.65	1.35–2.01	<.001	1.70	1.28–2.26	.0002
Smoking	1.42	1.01–1.60	.04	1.25	0.92–1.92	NS
Functional class 3-4	1.83	1.46–2.29	<.0001	1.24	0.91–1.68	NS
Cardiac medication	1.69	1.33–2.14	<.0001	1.32	0.96–1.82	NS
CVD	1.33	1.05–1.69	.02	1.40	0.98–1.98	NS
Glucose>6.0 mmol/L	1.27	1.06–1.52	.009	1.10	0.85–1.42	NS
Ambulatory ECG data						
SDNN<120 ms	1.29	1.09–1.53	.003	1.16	0.95–1.77	NS
Slope of HRV<-1.5	1.77	1.48–2.11	<.0001	1.74	1.42–2.13	<.001

Abbreviations as in Table 1.

*Determined in multivariate Cox regression analysis.

adjusted for age and sex in the Cox proportional hazards analysis in predictions of all-cause mortality. A history of previous myocardial infarction, angina pectoris, congestive heart failure and cerebrovascular disease, smoking, functional class, elevated blood glucose, SDNN <120 ms, and slope of the power-law regression <-1.50 were associated with all-cause mortality after adjustment for age and sex. When all the risk variables were included in the analysis, a steep slope of the power-law regression line (adjusted relative risk, 1.74; P<.0001) and a history of congestive heart failure (adjusted

relative risk, 1.70; P=.0002) were the only independent predictors (Table 2).

Predictors of Cardiac, Cerebrovascular, Cancer, and Other Causes of Death and Nonfatal Cardiovascular Events

Table 3 shows the significances and relative risks attached to various variables in predictions of cardiac and cerebrovascular deaths. After adjustment for age and sex, cardiac death was predicted by the same variables as all-cause mortality

TABLE 3. Significant Predictors of Cardiac and Cerebrovascular Mortality in Proportional Hazards Regression Analysis

	Age- and Sex-Adjusted Association With Mortality			Association With Mortality Adjusted for All Variables		
	Relative Risk	95% CI	P*	Relative Risk	95% CI	P*
Cardiac mortality						
Prior AMI	2.12	1.55–2.80	<.001	0.96	0.55–1.67	NS
Angina pectoris	1.91	1.50–2.44	<.001	1.50	0.87–2.56	NS
CHF	2.01	1.56–2.68	<.001	1.56	1.03–2.36	.03
Functional class 3-4	2.73	1.95–3.84	<.001	1.11	0.65–1.90	NS
Cardiac medication	2.39	1.33–2.14	<.001	1.68	0.92–3.10	NS
Glucose>6.0 mmol/L	1.64	1.25–2.06	.002	1.04	0.70–1.17	NS
SDNN<120 ms	1.46	1.09–1.80	.009	1.14	0.83–1.59	NS
VPBs≥10/h	1.52	1.11–1.97	.007	1.21	0.81–1.70	NS
Slope of HRV<-1.5	2.34	1.75–3.03	<.001	2.05	1.40–2.99	.0002
Cerebrovascular mortality						
Prior AMI	2.38	1.29–4.41	.005	1.17	0.52–2.62	NS
CHF	2.10	1.32–3.34	.002	1.72	0.86–3.44	NS
CVD	2.39	1.57–3.64	<.001	2.87	1.51–5.46	.001
Glucose>6.0 mmol/L	1.85	1.23–2.79	<.003	1.47	0.82–2.66	NS
SDNN<120 ms	1.71	1.13–2.57	.01	1.61	0.98–2.65	NS
Slope of HRV<-1.5	1.85	1.18–2.91	.008	2.84	1.71–4.70	.0001

Abbreviations as in Table 1.

except for smoking history and by the presence of ≥ 10 ventricular premature beats per hour on the 24-hour ECG recording. After adjustment for all risk variables, cardiac death was independently associated only with a steep slope of the regression line of HR variability (adjusted relative risk, 2.05; $P=.0002$) and a history of congestive heart failure (adjusted relative risk, 1.56; $P=.03$). The slope of the regression line of HR variability was also an independent predictor of cerebrovascular death (age- and sex-adjusted relative risk, 1.85; $P=.008$), which was also predicted by a history of cerebrovascular disease. None of the measures of HR variability had a univariate association with cancer death or various other nonvascular causes of death. When adjusted for age and sex, cancer death was predicted by current smoking (relative risk, 1.86; 95% confidence interval, 1.06 to 3.26; $P=.03$) and low cholesterol (<5.0 mmol/L) (relative risk, 1.70; 95% confidence interval, 1.02 to 2.88; $P=.04$), and various other causes of death were predicted only by functional disability (class 3 to 4) (relative risk 1.67, 95% confidence interval, 1.14 to 2.47, $P=.007$). Nonfatal cardiovascular events ($n=50$, consisting of 22 acute myocardial infarctions, 13 unstable angina pectoris, and 15 nonfatal strokes or transient ischemic attacks) were not predicted by measures of HR variability, (eg, slope -1.42 ± 0.20 versus -1.40 ± 0.19 in those with and without events). These events had a univariate association only with the baseline blood glucose (6.6 ± 4.2 mmol/L in subjects with events versus 5.4 ± 1.9 mmol/L in subjects without events, $P<.05$).

Correlations Between HR Variability and Other Risk Factors

The slope of the power-law regression line of HR variability showed weak correlations with age ($r=-.16$, $P<.01$) and blood fasting glucose concentration (-0.14 , $P<.05$) but no significant correlations with the other risk factors. SDNN was related to functional class (125 ± 36 ms in class 3 to 4 versus 140 ± 37 in class 1 to 2, $P<.01$), a history of prior myocardial infarction (136 ± 37 ms in patients without a prior infarction versus 120 ± 24 ms in those with a prior infarction, $P<.001$), and age ($r=-0.15$, $P<.001$).

Discussion

The results show that the power-law relationship of long-term HR variability is a more powerful predictor of mortality than conventional risk markers in elderly subjects. Concurrent with previous findings, common risk factors such as cholesterol, hypertension, and smoking were not strong predictors of death, confirming that the prognostic markers applicable to younger subjects do not perform as well among the elderly.¹⁻⁴

Twenty-Four-Hour HR Variability as a Predictor of Various Causes of Death

A previous study of a Framingham cohort also showed that the traditional short-term measures of HR variability are able to predict all-cause mortality in elderly subjects.¹⁵ In the present population, with a longer follow-up, traditional spectral and nonspectral measures did not emerge as independent predictors of survival because they were more closely related to other risk factors than the slope of the power-law relation-

ship of HR variability, which remained a powerful predictor of survival after adjustment for other variables.

The unique length of the present follow-up with a larger number of deaths than in previous studies^{5-7,15} allowed the evaluation of different causes of mortality. The slope of the power-law behavior of HR variability was specifically related to vascular causes of death, ie, cardiac and cerebrovascular death. HR variability has been previously shown to predict all-cause and cardiac mortality in patient populations with documented heart disease,⁵⁻⁷ but there has been no information on the prognostic role of HR variability as a predictor of cerebrovascular death. Present findings suggest that altered long-term HR behavior is not specifically related to cardiac death but reflects an increased risk for any acute vascular events leading to death. HR variability did not predict death from cancer or of various other causes showing that altered HR dynamics do not reflect the presence of an advanced malignant disease or frailty leading to mortality.

Speculated Mechanisms of Altered Long-term Behavior of Heart Rate as a Risk Factor for Mortality

The slope of the power-law relationship of HR variability computed over the ULF and VLF oscillations differs from the traditional measures of HR variability because it does not reflect the magnitude of HR variability but the distribution of spectral characteristics of R-R interval oscillations.^{7,14} The physiological background for the spectral distribution is not exactly known, but the observation of significantly steeper slope in denervated hearts suggests that it is mainly influenced by the autonomic input to the heart.⁷ The slope was found to be steeper in these elderly subjects than that previously observed in younger, healthy subjects,^{7,14} and it was weakly related to age despite the rather narrow age distribution, suggesting that aging itself results in progressive changes in the long-term spectral characteristics of HR variability. No changes in ULF power but a linear decline in VLF power has been observed with aging,¹⁶ which probably explains the steeper slope of the power-law regression line in the elderly.

Abnormalities in autonomic modulation of HR have been observed in various cardiovascular and cerebrovascular disorders,¹⁷⁻²⁰ and it is possible that altered cardiovascular neural regulation expressed by a steep slope of long-term HR dynamics may be a sign of an underlying subclinical vascular disease predisposing to mortality. Another potential explanation for the prognostic role of altered HR behavior is that it may reflect an impairment in the intrinsic physiological regulatory and adaptive systems, with aging leading to death during acute perturbations such as myocardial or cerebral ischemic events. This concept is supported by the observation that a steep slope did not predict the occurrence of nonfatal cardiovascular events. Experimental data also show that cardiovascular autonomic regulation plays an important role in occurrence of life-threatening arrhythmias during acute cardiac or cerebral ischemia.^{21,22}

From a mathematical point of view, it is noteworthy that the value of a slope of -1.5 turned out to be the optimum discriminator of mortality. In mathematics, the same bound-

ary (ie, slope of 1.5) is used to separate “1/f noise” (slope ≈ 1) and “1/f² noise” (slope ≈ 2). Both 1/f and 1/f² noise are well-characterized physical phenomena; eg, 1/f distributions have been demonstrated in various physical systems. The 1/f noise is less correlated than 1/f² noise, which reflects a very high degree of long-range temporal correlation. The present data show that the worst prognosis is seen in subjects with the highest degree of long-range temporal correlation in their HR dynamics.

Conclusions

The results show that 24-hour HR variability gives prognostic information beyond that obtained by traditional risk markers in a population of elderly subjects. Analysis of long-range correlation properties of HR data performed better than the traditional measures of HR variability in predicting the mortality, suggesting that dynamic analysis of HR behavior may give important complementary prognostic information in addition to conventional risk markers.

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