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Fractal analysis of heart rate variability and mortality in elderly community-dwelling people – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study

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Abstract

Aim—Fractal analysis of heart rate (HR) variability (HRV) has been used as a new approach to evaluate the risk of mortality in various patient groups. Aim of this study is to examine the prognostic power of detrended fluctuation analysis (DFA) and traditional time- and frequency-domain analyses of HR dynamics as predictors of mortality among elderly people in a community.

Methods—We examined 298 people older than 75 years (average age: 79.6 years) and 1-h ambulatory ECG was monitored. During the last 10 min, deep respiration (6-s expiration and 4-s inspiration) was repeated six times in a supine position. Time-domain and frequency-domain measures were determined by the maximum entropy method. Scaling exponents of short-term (<11 beats, alpha 1) and longer-term (>11 beats, alpha 2) were determined by the DFA method. Six estimates, obtained from 10-min segments, were averaged to derive mean values for the entire recording span. These average values were denoted Alpha 1 and Alpha 2, estimates obtained during the first 10-min segment Alpha 1 S and Alpha 2 S, and those during the last 10-min segment Alpha 1 E and Alpha 2 E, respectively. The LILAC study started on July 25, 2000 and ended on November

30, 2004. We used Cox regression analysis to calculate relative risk (RR) and 95% confidence interval (CI) for all-cause mortality. Significance was considered at a value of $P < 0.05$.

Results—Gender, age and Alpha 2E showed a statistically significant association with all-cause mortality. In univariate analyses, gender was significantly associated with all-cause mortality, being associated with a RR of 3.59 ($P = 0.00136$). Age also significantly predicted all-cause mortality and a 5-year increase in age was associated with a RR of 1.49 ($P = 0.01809$). The RR of developing all-cause mortality predicted by a 0.2-unit increase in Alpha 2E was 0.58 ($P = 0.00390$). Other indices of fractal analysis of HRV did not have predictive value. In multivariate analyses, when both Alpha 2E and gender were used as continuous variables in the same model, Alpha 2E remained significantly associated with the occurrence of all-cause mortality ($P = 0.02999$). After adjustment for both gender and age, a 0.2-unit increase in Alpha 2E was associated with a RR of 0.61 (95% CI: 0.424).90, $P = 0.01151$).

Conclusion—An intermediate-term fractal-like scaling exponent of RR intervals was a better predictor of death than the traditional measures of HR variability in elderly community-dwelling people. It is noteworthy that the longer-term (alpha 2) rather than the short-term fractal component (alpha 1) showed predictive value for all-cause mortality, which suggests that an increase in the randomness of intermediate-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore may also be associated with an increased risk of mortality.

Keywords

Fractal; Heart rate variability; Detrended fluctuation analysis; All-cause mortality; Elderly community-dwelling people

1. Introduction

Fractal analysis of heart rate (HR) variability (HRV) has been used as a new approach to evaluate the risk of mortality in various patient groups [1-3]. Several new methods have been developed to quantify complex HR dynamics and to complement the conventional measures of HR variability. These methods have provided powerful prognostic information in different populations, but their prognostic power has not been studied in elderly community-dwelling people. In this study, we examine the prognostic power of fractal detrended fluctuation analysis and traditional time- and frequency-domain analyses of HR dynamics as predictors of mortality among elderly people in a community.

2. Methods

2.1. Subjects and LILAC study design

We examined 298 people older than 75 years (average age: 79.6 years). One hour of ambulatory ECG recording was obtained during routine medical examination conducted each year in July. During the last 10 min, deep respiration (6-s expiration and 4-s inspiration) was repeated six times in a supine position. The data were processed for HRV using a Fukuda-Denshi Holter analysis system (SCM-280-3). Time-domain measures (CVRR, SDANN, rMSSD and pNN50) and frequency-domain measures (spectral power in the “very low frequency” - VLF: 0.003-0.04 Hz, “low frequency” - LF: 0.04-0.15 Hz, and “high frequency” - HF: 0.15-0.40 Hz regions, and LF/HF ratio) were determined. All indices were computed as averages over consecutive 5-min intervals. Spectral indices were obtained by the maximum entropy method (MEM) with the MemCalc/CHIRAM program (Suwa Trust Co., Ltd., Tokyo, Japan).

The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short- and intermediate-term RR intervals. The root-mean-squares fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the

size of the observation window on a log-log scale. The details of this method were shown elsewhere by Peng et al. [4]. The HR correlations were defined separately for short-term (<11 beats, alpha 1) and longer-term (>11 beats, alpha 2) RR interval data (scaling exponent). Six estimates of both alpha 1 and alpha 2, obtained from 10-min segments based on 4000 RR intervals, were averaged to derive mean values for the entire recording span. These average values were denoted Alpha 1 and Alpha 2, respectively. Estimates obtained during the first 10-min segment were denoted Alpha 1 S and Alpha 2 S, respectively, and those obtained during the last 10-min segment Alpha 1 E and Alpha 2 E, respectively.

2.2. Follow-up

The LILAC study started on July 25, 2000. Consultations were repeated every year (end of July, or beginning of August). In addition, one or two doctors of our team visited every 3 months and offered several kinds of health consultation regarding the rehabilitation of disordered functions, healthy lifestyle modifications, such as the promotion of complete smoking cessation, weight reduction, reduction of salt intake, moderation in the consumption of fruits and vegetables and alcohol intake, and advice in terms of medical prescriptions for the local general practitioner.

In this investigation, the follow-up ended on November 30, 2004. The follow-up time was defined as the time elapsed between the date of first (reference) examination and the date of all-cause mortality.

2.3. Statistical analysis

All data were analyzed with the Statistical Software for Windows (StatFlex Ver.5.0, Artec, Osaka, <http://www.statflex.net>). We used Cox regression analysis to calculate the unadjusted and adjusted relative risk (RR) and 95% confidence interval (CI) for all-cause mortality. To identify independent predictors of all-cause mortality, we used multivariate Cox regression analyses with stepwise selection. Variables included in the multivariate models were age, gender, body mass index (BMI) and HR variability indices. Significance was considered at a value of $P < 0.05$.

3. Results

The reference characteristics of the 298 subjects are given in Table 1. The sample comprised 120 men and 178 women. The mean age of the participants at entry was 79 years. The mean follow-up time was 1152 days, during which 30 subjects died (21 men and nine women). Out of the 298 participants, HR variability was analyzed in 260 subjects, excluding subjects with cardiac arrhythmias, such as atrial fibrillation and frequent atrial and ventricular ectopies. Out of the 260 subjects, fractal analysis of HR variability was done in 184 subjects.

Among the variables used in Cox proportional hazard models, gender, age and Alpha 2E showed a statistically significant association with all-cause mortality (Table 2). In univariate analyses, gender was significantly associated with all-cause mortality, being associated with a relative risk of 3.59 ($P = 0.00136$). Age also significantly predicted all-cause mortality and a 5-year increase in age was associated with a relative risk of 1.49 ($P = 0.01809$). The relative risk of developing all-cause mortality predicted by a 0.2-unit increase in Alpha 2E was 0.58 ($P = 0.00390$). Other indices of fractal analysis of HRV did not have predictive value. In multivariate analyses, when both Alpha 2E and gender were used as continuous variables in the same model, Alpha 2E remained significantly associated with the occurrence of all-cause mortality ($P = 0.02999$). After adjustment for both gender and age, a 0.2-unit increase in Alpha 2E was associated with a relative risk of 0.61 (95% CI: 0.42 to 0.90, $P = 0.01151$).

4. Discussion

The main finding of this study is that an intermediate-term fractal-like scaling exponent of RR intervals is a better predictor of death than the traditional measures of HR variability in elderly community-dwelling people. It is noteworthy that the longer-term (α_2) rather than the short-term fractal component (α_1) showed predictive value for all-cause mortality. This result contrasts with most previous studies reporting that a short-term fractal component was a better predictor in different patient populations [1-3]. It should also be kept in mind that in this study, a predictive value was found for α_{2E} , corresponding to the last 10 min of ambulatory ECG monitoring, when deep breathing was repeated in a supine position.

The advantages of fractal exponent analysis over traditional indices of HR variability have been well known. The higher sensitivity of this approach stems from its ability to detect abnormalities in HR behavior in cases where abrupt temporal changes in RR intervals occur in a window of time of seconds or minutes. This observation suggests that an increase in the randomness of intermediate-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore may also be associated with an increased risk of mortality.

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Table 1

Reference characteristics of the 298 subjects

Variables	Number	Mean	S.D.	Minimum	Maximum
Days Follow-up	298	1152.0	462.2	114.0	1578.0
Gender	298	0.403	0.491	0	1
Age	298	79.0	4.7	70.0	96.0
BMI	284	23.5	3.5	13.9	33.3
Average HR	273	74.4	12.4	44.0	117.0
CVRR	260	5.21	2.13	1.80	22.47
SDANN	258	37.9	13.8	12.9	109.3
rMSSD	261	23.6	17.3	5.2	169.6
pNN50	261	4.6	9.1	0	76.3
VLF	261	926.9	720.8	62.7	6124.0
LF	260	212.1	274.7	6.8	1898.7
HF	259	108.0	261.4	5.1	2717.1
L/H	260	3.02	1.97	0.32	10.99
Alpha 1	184	1.045	0.234	0.45	1.49
Alpha 2	184	1.054	0.121	0.58	1.33
Alpha 1 S	184	1.028	0.271	0.35	1.52
Alpha 2 S	184	1.060	0.185	0.56	1.51
Alpha 1 E	184	1.061	0.250	0.35	1.53
Alpha 2 E	184	1.099	0.202	0.36	1.73

Gender: $M = 1$, $F = 0$ (120 men and 178 women).

Table 2
Relative risk (RR) of the all-cause mortality in elderly community-dwelling people

Variables	Number	β	S.E. (β)	z-value	P-value	RR	95% CI
Gender	298	1.277	0.398	3.204	0.00136	3.59	1.64 7.83
Age (5)	298	0.080	0.034	2.364	0.01809	1.49	1.07 2.08
BMI	284	-0.049	0.054	0.905	N.S.		
Average HR	273	0.016	0.015	1.059	N.S.		
CVRR	260	0.055	0.088	0.622	N.S.		
SDANN	258	0.003	0.015	0.181	N.S.		
rMSSD	261	0.008	0.009	0.952	N.S.		
pNN50	261	0.012	0.017	0.721	N.S.		
VLF	261	0.000	0.000	0.775	N.S.		
LF	260	0.000	0.000	0.428	N.S.		
HF	259	0.000	0.000	0.030	N.S.		
L/H	260	-0.168	0.116	1.456	N.S.		
Alpha 1	184	-1.364	0.873	1.563	N.S.		
Alpha 2	184	-2.899	1.547	1.874	0.06090		
Alpha 1 S	184	-0.890	0.765	1.163	N.S.		
Alpha 2 S	184	-1.112	1.192	0.934	N.S.		
Alpha 1 E	184	-1.198	0.816	1.468	N.S.		
Alpha 2 E (0.20)	184	-2.760	0.956	2.886	0.00390	0.58	0.40 0.84
Alpha 2 E (0.2)	184	-2.079	0.958	2.170	0.02999	0.66	0.45 0.96
Gender adjusted							
Alpha 2 E (0.2)	184	-2.452	0.970	2.527	0.01151	0.61	0.42 0.90
Gender-, age-adjusted							

Gender: $M = 1$, $F = 0$ (120 men and 178 women).