# Fractal Analysis of Heart Rate Variability and Mortality After an Acute Myocardial Infarction

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**The recently developed fractal analysis of heart rate (HR) variability has been suggested to provide prognostic information about patients with heart failure. This prospective multicenter study was designed to assess the prognostic significance of fractal and traditional HR variability parameters in a large, consecutive series of survivors of an acute myocardial infarction (AMI). A consecutive series of 697 patients were recruited to participate 2 to 7 days after an AMI in 3 Nordic university hospitals. The conventional time-domain and spectral parameters and the newer fractal scaling indexes of HR variability were analyzed from 24-hour RR interval recordings. During the mean follow-up of 18.4 ± 6.5 months, 49 patients (7.0%) died. Of all the risk variables, a reduced short-term fractal scaling exponent ($\alpha_1$ <0.65), measured by detrended fluctuation analysis, was the most powerful predictor of mortality (univariate relative risk 5.05, 95% confidence intervals [CI] 2.87 to 8.89, p <0.001). A low scaling exponent $\alpha_1$ predicted death in the patients with and without depressed left ventricular function (p <0.001 and p <0.01, respectively). Several other HR variability parameters also predicted mortality in univariate analyses, but in a multivariate analysis after adjustments for clinical variables and left ventricular ejection fraction, $\alpha_1$ was the most significant independent HR variability index that predicted subsequent mortality (relative risk 3.90, 95% CI 2.03 to 7.49, p <0.001). Short-term fractal scaling analysis of HR variability is a powerful predictor of mortality among patients surviving an acute myocardial infarction.** 

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Fractal analysis of heart rate (HR) variability has been used as a new approach to evaluate the risk of mortality in various patient groups. In selected patient populations with depressed left ventricular function and/or heart failure, the decreased short-term fractal scaling exponent ($\alpha_1$), an index of qualitative fluctuation patterns of HR, has been shown to be a strong predictor of cardiac and total mortality.[1–4] So far, the value of fractal scaling analysis has not been documented in a consecutive series of post-acute myocardial infarction (AMI) patients. This prospective study was designed to assess the prognostic significance of fractal analysis of HR variability in a large sample size of consecutive patients who survived an AMI. The prognostic value of various indexes of HR variability was compared with various other risk factors.

## METHODS

**Study population:** A consecutive series of 806 patients were screened in 3 centers (Gentofte and Glostrup Hospitals, Copenhagen, Denmark; and Oulu University Hospital, Oulu, Finland) as part of the Nordic implantable cardioverter-defibrillator pilot study. This pilot study aimed to assess the predictive power of HR variability and left ventricular function as predictors of mortality. The results, including implantation of cardioverter-defibrillators in 33 patients, have been previously reported.[5] The patients were recruited to participate in the study during the first 7 days after an AMI. The diagnosis of AMI was based on an elevation of myocardial enzymes up to ≥2 times the upper limit of normal that could not be attributed to any other condition, and 1 or 2 of the following parameters: (1) chest pain or dyspnea lasting for ≥30 minutes, and (2) ischemic electrocardiographic changes on admission or any later change in the electrocardiogram caused by AMI. The exclusion criteria were advanced age (>75 years), unstable angina at recruitment, dementia, alcoholism, drug abuse, or nonsinus rhythm on the electrocardiogram, or any other condition that could impair the subject's capacity for informed consent. Patients who underwent coronary bypass surgery before measurements or were not discharged alive from the hospital were not included in the analysis. The study protocol was approved by the ethical

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**TABLE 1** Clinical Patient Characteristics

| | All Patients (n = 697) | Alive (n = 648) | Dead (n = 49) |
|---|---|---|---|
| Men/women | 521/176 (75%/25%) | 486/162 (75%/25%)§ | 35/14 (71%/29%) |
| Age (yrs, mean ± SD) | 61.2 ± 10.1 | 60.8 ± 10.1‡ | 67.4 ± 7.9 |
| Systemic hypertension | 300 (44%) | 272/367 (43%)* | 28/21 (58%) |
| Diabetes mellitus | 135 (20%) | 119/518 (19%)* | 16/33 (33%) |
| Previous myocardial infarction | 139 (20%) | 122/520 (19%)† | 17/32 (35%) |
| Non–Q-wave myocardial infarction‖ | 297 (44%) | 267/340 (44%)† | 30/17 (64%) |
| Anterior wall myocardial infarction¶ | 301 (45%) | 271/290 (48%)† | 30/11 (73%) |
| Thrombolytic therapy or primary coronary angioplasty | 329 (50%) | 317/312 (50%)‡ | 12/37 (25%) |
| Left ventricular systolic function | | | |
| Wall motion index (mean ± SD) | 1.53 ± 0.33 | 1.55 ± 0.32‡ | 1.33 ± 0.34 |
| Ejection fraction (%) (mean ± SD)# | 45.9 ± 9.9 | 46.5 ± 9.6 | 39.9 ± 10.2 |
| NYHA class at discharge** | | | |
| I–II | 534 (89%) | 506 (91%)‡ | 28 (65%) |
| III–IV | 67 (11%) | 52 (9%) | 13 (35%) |
| β blockers | 559 (84%) | 522 (85%)§ | 37 (79%) |
| ACE inhibitors or angiotensinogen II receptor antagonists | 272 (41%) | 246 (40%)* | 26 (55%) |
| Amiodarone | 8 (1%) | 7 (1%)§ | 1 (2%) |

*p <0.05; †p <0.01; ‡p <0.001; §p = NS.
‖Number of infarctions of indeterminate site (67).
¶Number of infarctions of indeterminate type (21).
#Ejection fraction calculated from wall motion index by multiplying with 30.
**New York Heart Association (NYHA) class was not assessed in all patients in 1 of the participating hospitals (data on 96 patients are therefore missing).
ACE = angiotensin-converting enzyme.

**TABLE 2** Various Heart Rate (HR) Variability Parameters in the Patient Groups Divided by Survival

| | All Patients (n = 697) | Alive (n = 648) | Dead (n = 49) |
|---|---|---|---|
| Nonspectral HR variability measures | | | |
| Mean RR interval | 898 ± 143 | 901 ± 144* | 859 ± 123 |
| SDNN | 94.5 ± 32.0 | 95.6 ± 32.1‡ | 79.4 ± 25.7 |
| Spectral measures | | | |
| ULF ln ($ms^2$) | 8.6 ± 0.7 | 8.6 ± 0.7* | 8.4 ± 0.7 |
| VLF ln ($ms^2$) | 6.5 ± 0.9 | 6.5 ± 0.9‡ | 5.8 ± 1.0 |
| LF ln ($ms^2$) | 5.4 ± 1.2 | 5.5 ± 1.2‡ | 4.6 ± 1.2 |
| HF ln ($ms^2$) | 4.7 ± 1.1 | 4.7 ± 1.1§ | 4.4 ± 1.2 |
| LF/HF ratio | 2.7 ± 2.1 | 2.7 ± 2.1* | 1.9 ± 2.1 |
| Fractal measures | | | |
| $\alpha_1$ | 1.00 ± 0.31 | 1.02 ± 0.30‡ | 0.76 ± 0.33 |
| $\alpha_1$ (edited) | 1.25 ± 0.24 | 1.26 ± 0.23‡ | 1.10 ± 0.32 |
| $\alpha_2$ | 1.08 ± 0.14 | 1.08 ± 0.13‡ | 1.01 ± 0.21 |
| $\alpha_2$ (edited) | 1.15 ± 0.11 | 1.14 ± 0.10§ | 1.16 ± 0.14 |
| $\beta$ | −1.28 ± 0.55 | −1.27 ± 0.56‡ | −1.44 ± 0.24 |

*p <0.05; †p < 0.01; ‡p <0.001; §p = NS.
Edited indicates analysis after editing for premature beats.
$\beta$ = slope of the power-law regression line.

committees of the institutions, and all the patients gave informed consent.

**Risk variables:** Left ventricular systolic function was measured with 2-dimensional echocardiography 2 to 7 days after the AMI. Wall motion index, an estimate of the left ventricular ejection fraction, was measured by a previously described method.[6,7] A 24-hour RR interval recording was carried out with a portable RR interval recorder (Polar Electro Co Ltd., Kempele, Finland) with a sampling frequency of 1,000 Hz[8–10] between days 5 and 14. All the RR interval tachograms went through a detailed manual editing process as previously described.[11,12] For fractal scaling analysis, this was performed in 2 steps: in the first phase, only the artifacts were edited off the recording (analysis of "unedited data"); the second analysis was performed on the data including only sinus beats ("edited data"). Recordings with <18 hours of data or <85% of qualified sinus beats were excluded. All the HR variability analyses were performed in the core laboratory, Oulu University, which has extended experience of RR interval editing and analysis.[11–13]

The time- and frequency-domain analyses of HR variability were performed according to the recommendation of the task force.[14] The SD of consecutive RR intervals (SDNN) was chosen as a time-domain index of HR variability. The power spectrum of HR variability was measured using fast-Fourier transform analysis in 4 frequency bands: <0.0033 Hz (ultra low frequency, ULF), 0.0033 to 0.04 Hz (very low frequency, VLF), 0.04 to 0.15 Hz (low frequency, LF), and 0.15 to 0.40 Hz (high frequency, HF). ULF and VLF components were computed over the entire recording interval. LF and HF components were computed from segments of 512 RR intervals. LF/HF ratio was calculated as the ratio of LF power (in square milliseconds) to HF power (in square milliseconds). For long-term fluctuations, the scaling exponent $\beta$ was computed to assess the power-law relation of HR variability as previously described.[15,16]

For short- and intermediate-term scaling properties

**TABLE 3** Predictors of All-cause Mortality in Univariate and Multivariate Analysis

| | Relative Risk | 95% CI | p Value |
|---|---|---|---|
| Univariate analysis | | | |
| Age >70 yrs | 3.16 | 1.80–5.53 | 0.000 |
| Diabetes mellitus | 1.96 | 1.08–3.54 | 0.027 |
| Previous myocardial infarction | 2.08 | 1.16–3.73 | 0.014 |
| No reperfusion therapy | 3.08 | 1.61–5.88 | 0.001 |
| Anterior wall myocardial infarction | 2.86 | 1.44–5.69 | 0.003 |
| Non–Q-wave myocardial infarction | 2.25 | 1.24–4.06 | 0.007 |
| NYHA class III-IV | 4.69 | 2.51–8.78 | 0.000 |
| Wall motion index <1.5 | 3.69 | 2.00–6.79 | 0.000 |
| Mean RR interval <815 ms | 2.14 | 1.22–3.76 | 0.008 |
| SDNN <65 | 2.37 | 1.32–4.28 | 0.004 |
| ULF (ln) <8.45 | 2.37 | 1.34–4.18 | 0.003 |
| VLF (ln) <5.30 | 3.70 | 1.99–6.87 | 0.000 |
| LF (ln) <3.85 | 3.50 | 1.85–6.59 | 0.000 |
| LF/HF ratio <1.45 | 3.75 | 2.11–6.67 | 0.000 |
| $\alpha_1$ <0.65 | 5.05 | 2.87–8.89 | 0.000 |
| $\alpha_1$ (edited) <1.00 | 4.09 | 2.31–7.23 | 0.000 |
| $\alpha_2$ <1.05 | 2.70 | 1.54–4.74 | 0.001 |
| $\beta$ <−1.55 | 3.09 | 1.66–5.74 | 0.000 |
| Multivariate analysis | | | |
| Age >70 yrs | 2.47 | 1.31–4.64 | 0.005 |
| NYHA class III-IV | 3.66 | 1.88–7.13 | 0.000 |
| Wall motion index <1.5 | 2.46 | 1.30–4.65 | 0.006 |
| ULF (ln) <8.45 | 2.05 | 1.06–3.98 | 0.033 |
| VLF (ln) <5.30 | 2.51 | 1.23–5.13 | 0.012 |
| LF (ln) <3.85 | 2.20 | 1.08–4.48 | 0.029 |
| LF/HF ratio <1.45 | 3.49 | 1.76–6.90 | 0.000 |
| $\alpha_1$ <0.65 | 3.90 | 2.03–7.49 | 0.000 |
| $\alpha_1$ (edited) <1.00 | 2.89 | 1.49–5.63 | 0.002 |
| $\beta$ <−1.55 | 2.21 | 1.11–4.44 | 0.025 |

CI = Confidence interval; other abbreviations as in Table 1.

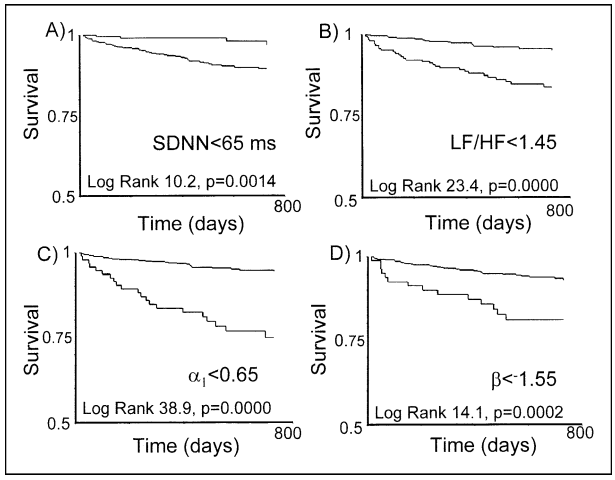


**FIGURE 1. Kaplan-Meier survival curves for various HR variability parameters. *(A)* SDNN. *(B)* LF/HF ratio spectral power (logarithmic conversion). *(C)* $\alpha_1$. *(D)* $\beta$ = 1/f power-law slope.**

of HR variability, the detrended fluctuation analysis (DFA) technique was used. This method detects the presence or absence of fractal-like scaling properties and has been validated for time series data. The details of this method have been previously described.[17–19] The correlation properties were measured both for short-term (≤11 beats, $\alpha_1$) and intermediate-term (>11 beats, $\alpha_2$) fluctuations of RR interval data.[17–19]

**Follow-up and end points:** The patients were followed for up to 2 years after the AMI, and they were routinely contacted via telephone at 6, 12, and 24 months after the AMI. The end point was all-cause mortality.

**Statistical analysis:** Data were analyzed using SPSS software (SPSS 10.0.1, SPSS Inc., Chicago, Illinois). Univariate comparisons of the baseline characteristics between the subjects who died and the survivors were performed with the chi-square test for categorical variables and with the 2-sample *t* test for continuous variables. The cut-off points for all predictive variables were determined by searching the value that maximized the statistically most significant hazard ratio obtained from the Cox regression analysis. The analysis was performed in fifth percentile steps below the median for each variable. Relative risk and 95% confidence intervals were calculated for each categorical variable as a predictor of all-cause mortality in the Cox regression model. To estimate the independent power of the variables in predicting mortality, the test results that had a univariate association with all-cause mortality ($p < 0.05$) were included in the Cox proportional hazards regression analyses after adjusting for clinical variables and wall motion index. Kaplan-Meier estimates of the distribution of times from baseline to death were computed, and log-rank analysis was performed to compare the survival curves between the groups. A p value <0.05 was considered significant. In addition, receiver-operating characteristic curves showing sensitivity as a function of the complement of specificity were generated to compare the predictive power of various prognostic variables.

## RESULTS

Of the screened population of 806, 697 patients with analyzable HR variability measurements were eligible for the study. The most common reason for a missing HR variability result was a technically unsuccessful recording (with artifacts or ectopy). Patient characteristics are listed in Table 1. By the mean follow-up of 18.4 ± 6.5 months (4 to 24), 49 patients (7.0%) had died and 648 (93%) were still alive.

**Univariate and multivariate predictors of mortality:** Table 1 lists the prevalence of clinical features and Table 2 lists the various HR variability parameters in the survivors and those who died. The relative univariate risk of the clinical variables and the test results as predictors of all-cause mortality are listed in Table 3. Conventional clinical risk factors were associated with an unfavorable prognosis during the follow-up. Most of

**TABLE 4** Sensitivity, Specificity, and Predictive Accuracy of Abnormal Values of Various Risk Variables

| Variable | Below Cut-off Point n, % | Sensitivity | Specificity | PPA | NPA | Area Under ROC Curve |
|---|---|---|---|---|---|---|
| Wall motion index <1.5 | 256 (37%) | 68% | 65% | 13% | 97% | 0.695‡ |
| RR interval <815 ms | 205 (30%) | 45% | 72% | 11% | 94% | 0.588* |
| SDNN <65 | 132 (19%) | 35% | 82% | 13% | 94% | 0.649† |
| ULF (ln) <8.45 | 271 (39%) | 59% | 62% | 11% | 95% | 0.619† |
| VLF (ln) <5.30 | 69 (10%) | 29% | 91% | 20% | 94% | 0.698‡ |
| LF (ln) <3.85 | 69 (10%) | 27% | 91% | 19% | 94% | 0.700‡ |
| LF/HF ratio <1.45 | 207 (30%) | 61% | 73% | 15% | 96% | 0.678‡ |
| $\alpha_1$ <0.65 | 93 (14%) | 43% | 89% | 23% | 95% | 0.716‡ |
| $\alpha_1$ (edited) <1.00 | 99 (14%) | 41% | 88% | 20% | 95% | 0.644† |
| $\alpha_2$ <1.05 | 209 (30%) | 53% | 71% | 12% | 95% | 0.629† |
| $\beta$ <−1.55 | 80 (12%) | 29% | 90% | 18% | 94% | 0.657‡ |

*p <0.05; †p <0.01; ‡p <0.001.
NPA = negative predictive accuracy; PPA = positive predictive accuracy; ROC = receiver-operating curve.

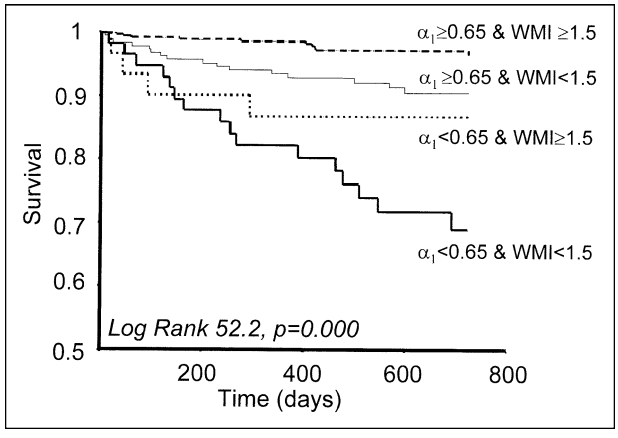


**FIGURE 2. Kaplan-Meier survival curves of patients divided into different subgroups according to $\alpha_1$ and wall motion index (WMI).**

the HR variability parameters tested were associated with increased all-cause mortality, the reduced short-term scaling exponent $\alpha_1$ was the most powerful univariate predictor. Its predictive value was higher when measured from unedited HR variability data instead of fully edited data. The survival curves obtained from the different HR variability analyses are shown in Figure 1. Of the several HR variability parameters independently predicting all-cause mortality in multivariate analysis, the reduced short-term fractal scaling exponent $\alpha_1$ measured from unedited data remained the most powerful risk marker, followed by a decreased LF/HF ratio (Table 3).

**Accuracy of HR variability parameters as predictors of mortality:** The sensitivity, specificity, and predictive accuracy of various risk indicators as predictors of all-cause mortality are listed in Table 4. Among the different HR variability measures, a reduced short-term scaling exponent $\alpha_1$ had the highest positive predictive accuracy. The patients were divided into 2 groups based on their left ventricular systolic function, and the predictive power of the short-term scaling exponent was analyzed in each group. Reduced values of $\alpha_1$ predicted a significantly increased risk of mortality in both groups (Figure 2).

## DISCUSSION

The main finding of this prospective multicenter study was that fractal analysis of HR variability provides prognostic information beyond that attainable from the clinical variables and the degree of left ventricular dysfunction in a consecutive series of post-AMI patients. The predictive power of the short-term fractal scaling exponent surpassed the traditional time- and frequency-domain indexes of HR variability in risk stratification. It was of particular note that the reduced short-term scaling exponent also predicted mortality in patients without significant impairment of left ventricular function.

**Traditional HR variability parameters as predictors of mortality:** Numerous previous studies assessing the prognostic power of HR variability indexes, such as SDNN and various spectral components of HR variability, have shown that these parameters predict mortality when measured in the convalescent phase after an AMI.[20–26] Concurrent with these results, most of the conventional HR variability parameters used here were also able to predict mortality in the univariate analysis, but after adjustment for the clinical variables and left ventricular function, their predictive power was somewhat lower than that reported in previous studies.

There are some salient differences between the present and previous observational studies that may partly explain the substantially lower independent predictive power of the traditional HR variability indexes in this study. The original studies showing the association between the reduced HR variability and mortality rates are from the prethrombolytic era.[20,21] Since the early 1980s, both the medical and invasive treatments of post-AMI patients have significantly changed, because $\beta$ blockers, angiotensin-converting enzyme inhibitors, and revascularization are now used more frequently, resulting in much lower mortality figures. More recent studies, such as the Automatic Tone and Reflexes After Myocardial Infarction (ATRAMI) study and the study assessing postectopic turbulence, may also suffer from obvious selection bias, because they did usually include consecutive post-AMI patient populations.[24–27]

**Fractal analysis of HR variability and mortality:** The reduced short-term fractal scaling exponent was initially observed in patients with congestive heart failure.[17,27] In subsequent studies, the reduced scaling exponent was found to provide prognostic information among patients with depressed left ventricular function.[1–4] The present findings broaden the application of the short-term scaling exponent as a risk stratifier of mortality beyond the patients with impaired left ventricular function to more general post-AMI populations. Further work will show if postectopic turbulence analysis of HR variability will yield even more powerful prognostic information in addition to fractal analysis techniques.Scaling exponents obtained by detrended fluctuation analysis quantify the relations of HR fluctuations at different scales. Low exponent values correspond to dynamics where the magnitude of beat-to-beat HR variability is close to the magnitude of longer term variability. In contrast, high exponent values correspond to dynamics where the magnitude of long-term variability is substantially higher than beat-to-beat variability. Exponent values correlate with normalized spectral measures in controlled situations, and the LF/HF spectral ratio is closely related to the short-term fractal scaling exponent in controlled external contexts with a fixed respiratory rate.[29] However, the correlation is weaker in "free-running" ambulatory conditions, because fractal analysis provides precise information on the scaling properties of HR fluctuations over highly segmented time windows, whereas conventionally computed spectral measures only vaguely represent HR fluctuations in predetermined time windows.[30] An advantage of fractal analysis over the traditional analysis techniques is that scaling exponents can also be analyzed without removing or replacing the RR intervals caused by ectopic beats.

The physiologic background of abnormal fractal correlation properties associated with an increased risk of dying has not been fully established. However, there is increasing evidence to support the role of sympathetic activation behind this impairment. High norepinephrine levels, indicative of sympathoexcitation, have been observed to be related to random RR interval dynamics in patients with heart failure.[31] Furthermore, intravenous infusion of norepinephrine has been shown to lead to the reduced short-term fractal scaling exponent.[31] These observations suggest that an increase in the randomness of short-term HR behavior may be a specific marker of neurohumoral and sympathetic activation and therefore is also associated with an increased risk for adverse cardiovascular events.

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