

Effects and Significance of Premature Beats on Fractal Correlation Properties of R-R Interval Dynamics

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Background: Premature beats (PBs) have been considered as artifacts producing a bias in the traditional analysis of heart rate (HR) variability. We assessed the effects and significance of PBs on fractal scaling exponents in healthy subjects and patients with a recent myocardial infarction (AMI).

Methods: Artificial PBs were first generated into a time series of pure sinus beats in 20 healthy subjects and 20 post-AMI patients. Thereafter, a case-control approach was used to compare the prognostic significance of edited and nonedited fractal scaling exponents in a random elderly population and in a post-AMI population. Detrended fluctuation analysis (DFA) was used to measure the short-term (α_1) and long-term (α_2) fractal scaling exponents.

Results: Artificial PBs caused a more pronounced reduction of α_1 value among the post-AMI patients than the healthy subjects, for example, if >0.25% of the beats were premature a >25% decrease in the α_1 was observed in post-AMI patients, but 4% of the premature beats were needed to cause a 25% reduction in α_1 in healthy subjects. Both edited (1.01 ± 0.31 vs 1.19 ± 0.27 , $P < 0.01$) and unedited α_1 (0.71 ± 0.33 vs 0.89 ± 0.36 , $P < 0.05$) differed between the patients who died ($n = 42$) and those who survived ($n = 42$) after an AMI. In the general population, only unedited α_1 differed significantly between survivors and those who died (0.96 ± 0.19 vs 0.83 ± 0.27 , $P < 0.05$).

Conclusions: Unedited premature beats result in an increase in the randomness of short-term R-R interval dynamics, particularly in post-AMI patients. Premature beats must not necessarily be edited when fractal analysis is used for risk stratification.

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heart rate; fractal correlation; premature beats

Spectral and statistical measures of heart rate variability (HRV) provide prognostic information on patients after an acute myocardial infarction.¹⁻³ However, these conventional methods may not provide adequate information on the complexity that lies inside beat-to-beat variability. Several new methods based on chaos and fractal theory have been developed to obtain approaches in quantifying the dynamic properties of R-R interval time series.⁴⁻⁹ It has been suggested that nonlinear HRV methods can provide important information on the dynamics of the heart rate variability in various clinical settings.¹⁰⁻¹⁴ In particular, detrended fluctuation analysis (DFA) of R-R interval data has been of increasing interest. Analysis of the short-term fractal scaling exponent (α_1) has provided prognostic information in many patient populations.^{11,13,14}

Most ECG recordings include technical or biological artifacts that cause a bias in the reliable mea-

surement of HRV. Premature beats have been commonly considered as one source of error in the HRV analysis and several methods of handling and editing the artifacts and premature beats in the HRV data have been developed and tested.¹⁵⁻³¹ It has been recently suggested that premature beats may have an important role in the new dynamic analysis of R-R interval behavior, and should perhaps be included in the analyses, because they represent the real beat-to-beat R-R interval time series.^{13,14} However, the true effects of the premature beats on the nonlinear HR variability measures are largely unknown.

The purpose of the present study was to provide more information on the effects of the premature beats on the fractal scaling exponent α_1 and α_2 in two different populations, that is, among subjects without evidence of structural heart disease and among patients with a recent myocardial

infarction (AMI). We tested the hypothesis that the same amount of premature beats may have quantitatively different effects on nonlinear indices of HRV among the healthy subjects and patients with a recent myocardial infarction. We also tested, which of the many editing methods of premature beats is most suitable for fractal analysis of HRV. Finally, we assessed whether the short-term and long-term fractal scaling exponents α_1 and α_2 measured either from original R-R interval time series including the premature beats or from the R-R interval data after editing the premature beats separates the patients or subjects who remain alive from those who experienced a cardiac death during the follow-up.

STUDY POPULATION AND METHODS

The effects of the artificial premature R-R intervals on nonlinear HRV measures were studied from data sets of 8000 R-R intervals with pure sinus beats. Twenty R-R interval time series from 15 healthy subjects with no history of heart disease were selected from a previously described population of 114 healthy subjects³² and 20 R-R interval time series of 15 patients who had survived an AMI. The details of the post-AMI population have been described elsewhere.³³ Mean age of the healthy subjects was 45 ± 11 years and that of post-AMI patients 54 ± 5 years. General R-R interval variation was measured by the standard deviation of all normal R-R intervals (SDNN) and it was significantly lower ($P < 0.001$) among the post-AMI patients (85 ± 35 ms) than among the healthy subjects (175 ± 50 ms).

The effects of the real premature beats on the nonlinear HRV measures were studied from 24-hour R-R interval data of post-AMI patients and from 24-hour R-R interval data of a random elderly population. Forty-two post-AMI patients, who died during the follow-up of 14 ± 8 months, and 42 post-AMI patients matched with age, sex, functional class, and ejection fraction, who were alive after the follow-up, were selected from a previously described post-AMI population.³³ Beta-blocker drugs were given to 80 patients (95.2%), digoxin treatment was given to 8 patients (9.5%), and a calcium antagonist to 10 patients (11.9%). Forty-two healthy elderly subjects, who died during the follow-up of 120 months and 42 controls, who were alive, matched with age, sex, and functional class were

selected from a large survey of the health status of the elderly in the city of Turku, Finland. The details concerning enrollment, diagnosis, and follow-up of this random sample of 480 people aged 65 or more, who were living in the community from the register of the Social Insurance Institution have been described elsewhere.^{34–36} None of the 42 healthy elderly subjects that were included in this study were taking medication. Mean age of the selected elderly healthy subjects was 72 ± 4 years and that of post-AMI patients 69 ± 8 years. All deaths in both study populations were classified as cardiac deaths. General R-R interval variation was measured by SDNN and it was significantly lower ($P < 0.001$) also in this post-AMI group (81 ± 29 ms) compared to that of the elderly subjects (139 ± 35 ms).

The measurements of the all the 8000 R-R interval data were done with a RR recorder, a real-time microprocessor QRS detector system³⁷ (Polar Electro Oy, Kempele, Finland). The 24-hour electrocardiographic recordings were performed with a portable two-channel tape recorder (Oxford Medilog, Oxford, UK) with a sampling frequency of 256 Hz. Measured R-R intervals were saved in a computer disk for additional processing.

Artificial ectopic beats were generated into the tachograms of 8000 R-R intervals that included only pure sinus beats. Single premature beats followed by a compensatory pause were uniformly distributed over the whole R-R interval tachograms in random places. Ectopic beats with compensatory pauses replaced the original sinus beats so that the number of the R-R intervals remained the same and the tachograms were not shifted. Between two generated ectopic beats there always existed at least three pure sinus beats. Several levels of ectopy were used: amount of ectopy varied from 0.125% to an ectopy level where 35% of the R-R intervals were qualified as ectopic beats with compensatory pauses. Three different types of prematurity indexes were used so that the premature beats and the compensatory pauses differed by 30%, 20%, or 10% compared to previous normal R-R interval. Only one type of prematurity was used at a time. Insertion of the artificial premature beats in random places was done three times to obtain an average effect of the ectopy insertion on the nonlinear HRV parameters. The analyses of the fractal scaling exponents were performed for original data with pure sinus beats and for data with different amount of artificial premature beats.

The performance of four different editing methods in the fractal analysis of HRV was studied by editing the generated artificial premature beats with four different methods: deletion, interpolation of degree zero, interpolation of degree one, and cubic spline interpolation. Deletion removes the non-normal R-R intervals, interpolation of degree zero replaces the edited R-R intervals with a local average of the previous accepted normal R-R intervals. The local nonectopic neighborhood for the interpolation of degree 0 was three R-R intervals in this study. Interpolation of degree 1 replaces the R-R intervals with the points obtained from a fitted straight line over the edited R-R intervals. The basic idea of the cubic spline interpolation is to obtain smooth curves through a number of points. The coefficients of the cubic polynomials are fitted so that the curve passes through the data points without discontinuities. Cubic spline interpolation was computed over the ectopic beats from the local nonectopic neighborhood. The analyses of the fractal scaling exponent α_1 and α_2 were performed for original data with no premature beats or editing and for data with different amount of edited premature beats.

For all 24-hour data the preediton of artifacts was done with the interpolation of degree 0. First, premature beats were left unedited and secondly, premature beats were edited with the interpolation of degree 0. The analyses of the fractal scaling exponent α_1 and α_2 were performed for preedited data including premature beats and for data with edited premature beats.

Fractal Analysis of Heart Rate Variability

Detrended fluctuation analysis was performed and the scaling exponents α_1 and α_2 were computed to quantify the fractal scaling properties of short-term and intermediate-term R-R intervals time series. Detrended fluctuation analysis is a modified root mean square analysis of random walk and it quantifies the absence or presence of the fractal correlation properties of the heart rate. The details of this method have been described elsewhere.³⁸ The HR correlation properties were estimated for both short-term (≤ 11 R-R intervals, α_1) and for long-term (> 11 R-R intervals, α_2) R-R interval data.

For the data of 8000 R-R intervals the analyses of the fractal scaling exponents were computed over the whole segment and for the 24-hour data the analysis were done in 8000 R-R interval segments

to achieve an average value for the entire recording period.

Power Spectrum of HRV

The power spectrum of the HRV was computed for the data of 8000 R-R intervals with premature beats to observe the effects of the premature beats on power spectra in post-AMI and healthy subject population. Fast Fourier spectrum computation was used.

Statistical Methods

Independent samples *t* test was used to analyze the differences of the fractal scaling exponent values in patients who died and those who remained alive during the follow-up. Differences were analyzed in both post-AMI and general population. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Performance of Editing Methods

Figure 1 shows the performance of different editing methods in the analysis of the fractal scaling exponents α_1 and α_2 . In the α_1 analysis, the interpolation of degree 0 performed best in editing the artificial ectopic beats in both AMI patients and in healthy subjects. In α_2 analysis, the cubic spline interpolation produced the smallest error for the healthy subjects, but for the AMI patients the best performance of editing in the α_2 analysis was achieved with the interpolation of degree one.

Effects of the Generated Artificial Premature Beats

Figure 2 shows the effects of the artificial premature beats on the analysis of the fractal scaling exponents α_1 and α_2 . The analysis of the α_1 was more sensitive to the insertion of the premature beats in the AMI patients compared to healthy subjects. Even a small amount of ectopy insertion produced a large decrement in α_1 values with all the three types of the artificial premature beats. Only 0.25% of artificial premature beats of 20% prematurity produced over 25% decrease in the α_1 values in the post-AMI data, but in the healthy subjects more than 4% of artificial premature beats of 20% prematurity were needed to produced over 25% decrease in the α_1 values. In the post-AMI patients,

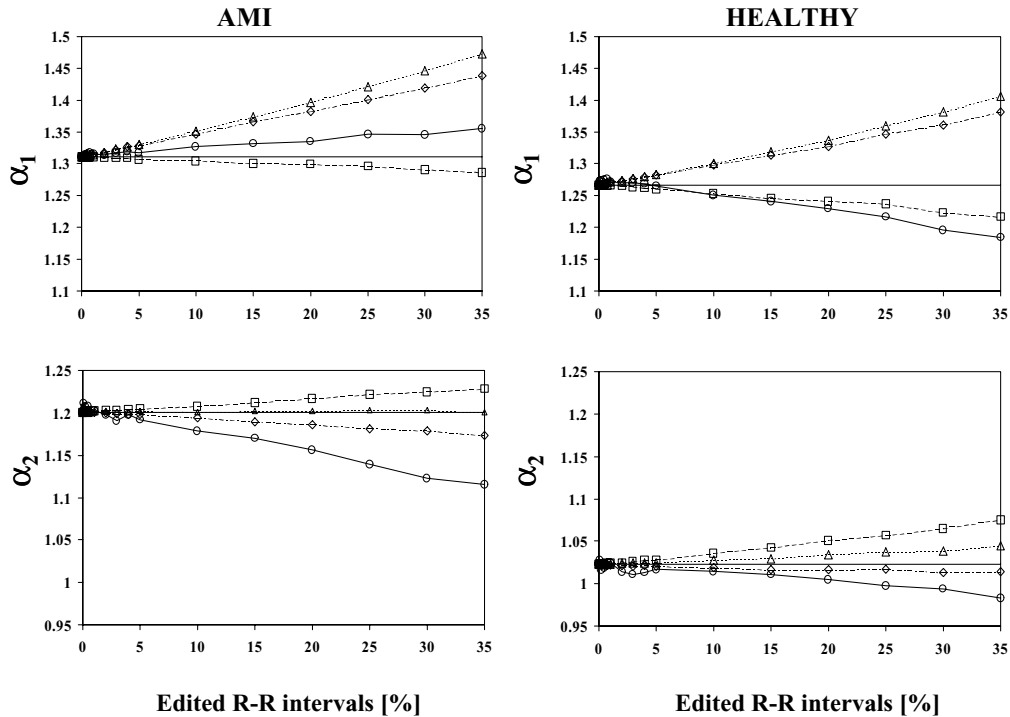


Figure 1. Effects of four different editing methods on the values of the fractal scaling analyses for the R-R interval data of post-AMI patients and healthy subjects. Mean values of the α_1 and α_2 analyses are in function of the amount of the edited R-R intervals. α_1 and α_2 indicate the scaling exponents analyzed by detrended fluctuation analysis from short and intermediate time windows respectively. The symbols indicate following editing methods: — = original values, —○— = deletion, ---□--- = interpolation of degree 0, ---△--- = interpolation of degree 1, and ---◇--- = cubic spline interpolation.

only 1% of artificial premature beats of 20% prematurity decreased the α_1 values under 0.75, while in the healthy patients the amount of 10% premature beats were needed to reduce the α_1 values under 0.75. Also, in the α_2 analysis the effects of the ectopy addition were more remarkable in the AMI patients compared to the healthy subjects. Figure 3 shows effects of the artificial premature beats on the HRV power spectrum of (1) a post-AMI and (2) a healthy subject. Already with a small inclusion of premature beats the power spectrum of a post-AMI patient included a larger degree of false frequency components especially in the higher frequency areas compared to the power spectrum of a healthy subject.

Effects of the Real Premature Beats on Fractal Scaling Analysis of 24-Hour Data

Comparisons of the α_1 and α_2 analysis in the post-AMI patients and in the elderly population between

those who died and those who survived during the follow-up are shown in Tables 1 and 2. In post-AMI, both edited and unedited α_1 values differed between survivors and nonsurvivors ($P < 0.01$ for edited, and $P < 0.05$ for unedited). In the general population, there were no significant differences between those who died and the survivors in the edited α_1 value. However, α_1 analyzed from the unedited data differed significantly between the elderly subjects who survived or experienced cardiac death ($P < 0.05$). In the analysis of α_2 , there was no significant difference between the survivors and those who died either in post-AMI or general population.

DISCUSSION

Time and frequency domain analysis of HRV is typically based on the assumption that various indices of HRV can describe the input of the autonomic nervous system on the sinus node.

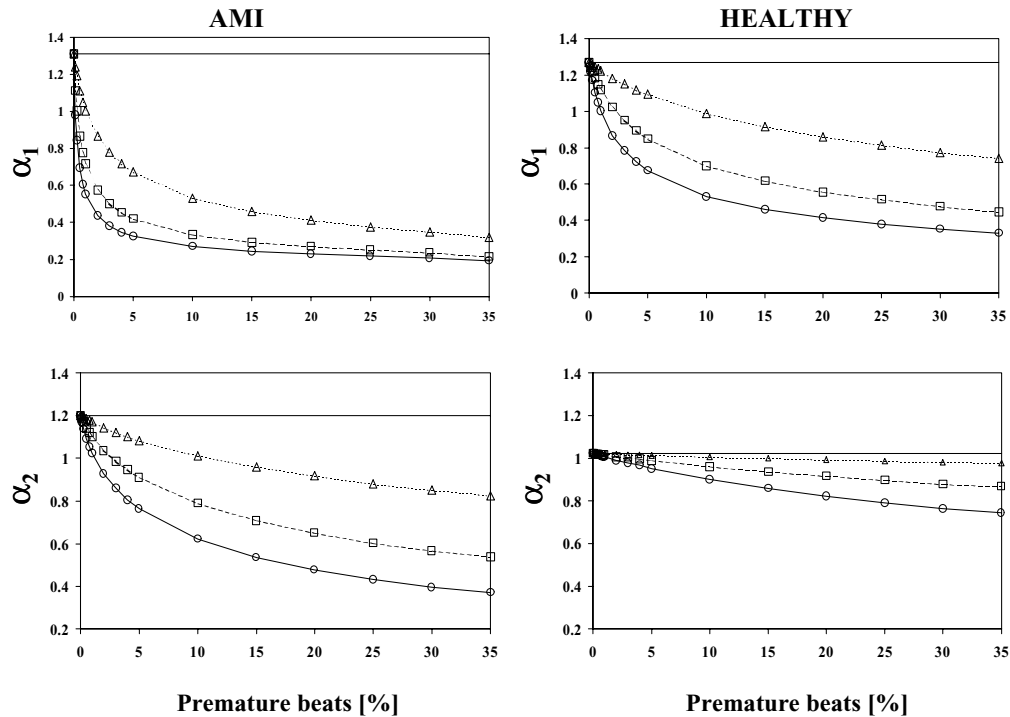


Figure 2. Effects of the artificial premature beats on fractal scaling analysis in post-AMI patients and healthy subjects. Mean values of the α_1 and α_2 analyses are in function of the amount of the premature beats. α_1 and α_2 indicate the scaling exponents analyzed by detrended fluctuation analysis from short and intermediate time windows respectively. The symbols indicate following prematurity: —○— = original (0% premature beats), —○— = 30% prematurity, ---□--- = 20% prematurity, and ---△--- = 10% prematurity.

Therefore, the ectopic beats are traditionally deleted and replaced or edited by artificial R-R intervals. Similar assumption may not deal with the analysis of dynamic behavior of R-R intervals by methods based on nonlinear dynamics, however. Unlike the traditional measures of HRV from Holter recordings containing ectopic beats, nonlinear analysis methods may describe true R-R interval dynamics without deletion and replacement of real R-R intervals caused by ectopic beats. The present study was designed to assess the effects of premature beats on fractal scaling exponents analyzed by the DFA methods. We chose this particular analysis method because the short-term fractal scaling exponent has provided important prognostic information in various patient populations.

The following main observations were made in this study. First, premature beats cause quantitatively different effects on short-term scaling exponent among the healthy subjects and post-AMI patients. Second, various editing methods may have divergent effects on fractal scaling exponents. In-

terpolation of degree 0 appeared to be the most suitable for editing of premature beats and artifacts when short-term scaling exponent is analyzed by the DFA method. Finally, the nonedited short-term scaling exponent provided prognostic information both in the post-AMI population and in the random general population.

Effects of Premature Beats on Fractal Scaling Exponents

Analysis of fractal-like HR behavior by the DFA methods has shown that healthy subjects show only little inter-individual variation in the short-term scaling exponent, its values being between 1.0 and 1.3. The present study showed that a relatively large amount of premature beats is needed before this normal fractal-like HR behavior is broken down toward more random dynamics in the subjects without an evidence of structural heart disease. On the contrary, in post-AMI patients even a

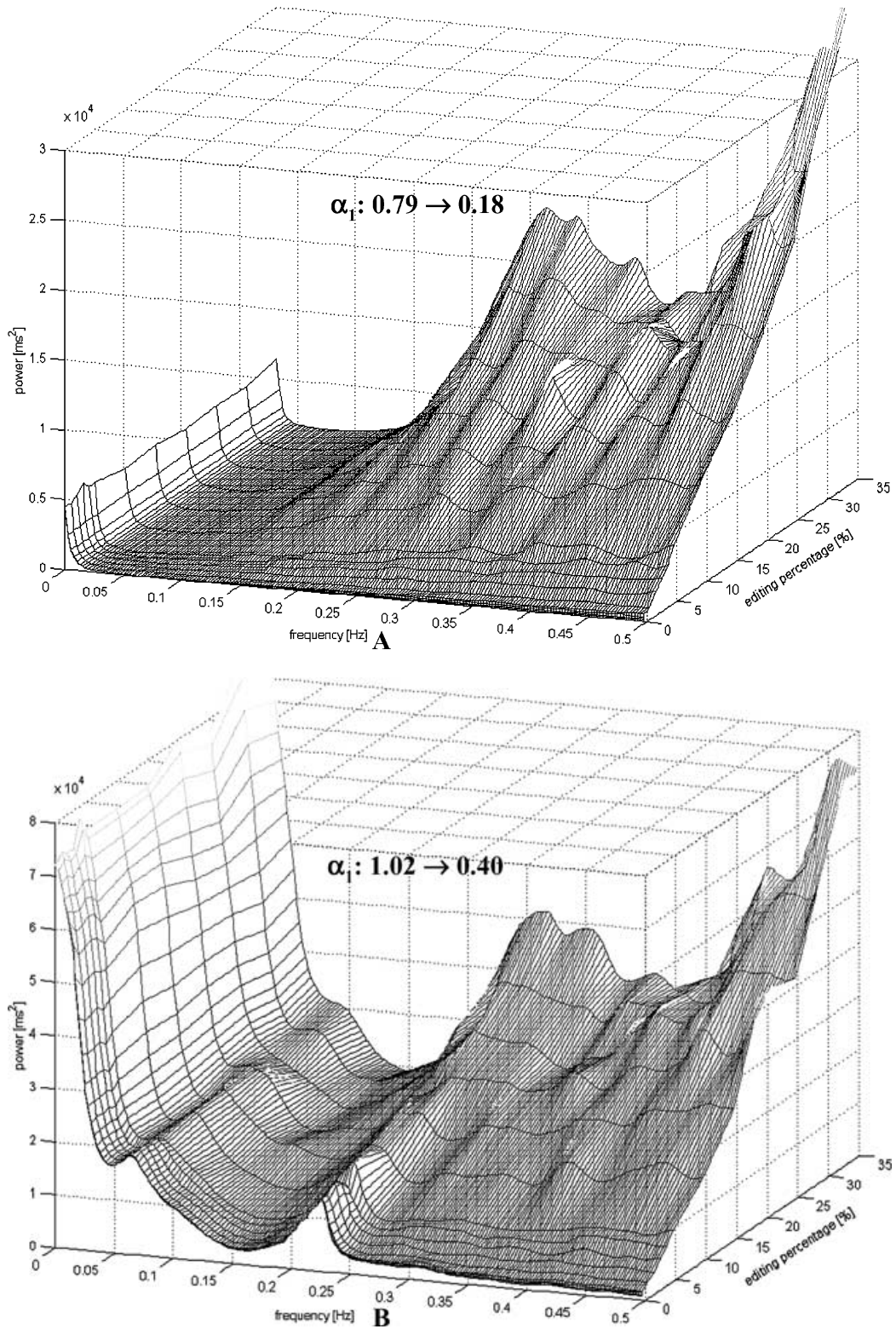


Figure 3. HRV power spectrum of (A) a post-AMI patient and (B) a healthy subject in function of the percentage of the artificial premature beats. Notice a different scaling in (A) and (B) due a different intensity of the spectral components.

Table 1. Measures of HR Dynamics Among the Post-Infarct Patients Who Died Due to Cardiac Causes During the Follow-up and Among the Matched Survivors

Clinical Variables	Dead (n = 42)	Alive (n = 42)	P Value
Age	69 ± 8	68 ± 8	NS
Men/women	26/16	26/16	NS
EF (%)	39 ± 12	42 ± 10	NS
NYHA-class II-III	67%	67%	NS
Number of premature beats/hour	26 ± 42	32 ± 68	NS
Measures of HR dynamics			
SDNN	76 ± 25	87 ± 32	NS
α_1 -unedited	0.71 ± 0.33	0.89 ± 0.36	0.05
α_1 -edited	1.01 ± 0.31	1.19 ± 0.27	0.01
α_2 -unedited	1.08 ± 0.20	1.09 ± 0.16	NS
α_2 -edited	1.21 ± 0.11	1.17 ± 0.12	NS

Values are expressed as mean ± standard deviation unless otherwise indicated.

EF = ejection fraction; NYHA = New York Heart Association Classification; SDNN = standard deviation of all R-R intervals; α_1 = short-term scaling exponent; α_2 = long-term scaling exponent; unedited = analysis of fractal measures of R-R interval variability including the premature beats; edited = analysis of fractal measures of R-R interval variability after editing of the premature beats.

small amount of premature beats resulted in random R-R interval dynamics.

There is an obvious explanation why a smaller amount of premature beats is needed in post-AMI patients to break down the normal fractal-like R-R interval dynamics. The post-AMI patients showed a smaller overall HRV, measured by SDNN, as well as smaller beat-to-beat R-R interval oscillations, measured by the high-frequency spectral component. Figure 3 shows how a HRV power spectrum of (1) a post-AMI and a (2) healthy subject changes by the inclusion of the artificial premature beats. It can be seen that in a post-AMI patient already a small amount of premature beats causes an extensive increase in the high frequencies of the power spectrum. In a healthy subject a larger amount of premature beats is required to cause a similar effect in the power spectrum. The scaling exponent α_1 is obtained from the slope of the logarithmic fluctuation function versus logarithmic R-R intervals. Therefore, α_1 describes the "roughness" of the R-R interval time series in the pre-defined time window. A larger value of the α_1 means a smoother signal.

Table 2. Measures of HR Dynamics Among the Healthy Subjects Who Died During the Follow-Up and Among the Matched Survivors

Clinical Variables	Dead (n = 42)	Alive (n = 42)	P Value
Age	73 ± 4	72 ± 4	NS
Men/women	23/19	23/19	NS
NYHA-class II-III	90%	90%	NS
Number of premature beats/hour	23 ± 28	14 ± 17	NS
Measures of HR dynamics			
SDNN	133 ± 38	144 ± 32	NS
α_1 -unedited	0.83 ± 0.27	0.96 ± 0.19	0.05
α_1 -edited	1.10 ± 0.18	1.16 ± 0.15	NS
α_2 -unedited	1.10 ± 0.12	1.11 ± 0.09	NS
α_2 -edited	1.17 ± 0.08	1.14 ± 0.09	NS

Values are expressed as mean ± standard deviation unless otherwise indicated.

NYHA = New York Heart Association Classification; SDNN = standard deviation of all R-R intervals; α_1 = short-term scaling exponent; α_2 = long-term scaling exponent; unedited = analysis of fractal measures of R-R interval variability including the premature beats; edited = analysis of fractal measures of R-R interval variability after editing of the premature beats.

Methods of Editing

In the α_1 analysis of the short-term data, the best performance of editing was achieved with the interpolation of degree 0 in both the post-AMI and the healthy population. If a large number of R-R intervals are edited with the interpolation of degree one or spline interpolation the α_1 value increases because of a smoothing effect of the spline interpolation on the R-R interval time series. The deletion method conversely decreases the α_1 value by increasing the "roughness" of the signal. This may happen with the R-R time series with high beat-to-beat variability (healthy subjects). But for the time series with a low R-R variability (AMI patients) the effects of the deletion method can even be opposite: the deletion method may produce an increase in the α_1 value by removing only few high frequency fluctuations (smoothing effect) that may appear. The effects of different editing methods on the HRV power spectrum analysis have been reported earlier by Salo et al.¹⁵ Deletion was found to be the most unsuitable editing method for the HRV power spectrum analysis. Interpolation methods were found to perform better in editing process compared to deletion, however, interpolation methods did cause a low-pass filtering effect by

smoothing the tachograms.¹⁵ Overall, the editing methods seem to have a larger magnitude on power spectral components than on fractal scaling exponents studied here.

Edited and Unedited α_1 and Mortality

The subjects of the general population who subsequently died due to cardiac problems had a lower short-term scaling exponent than those who survived when the analysis was done from the real R-R interval data including the premature beats. The edited short-term scaling exponent or the number of ectopic beats itself could not separate the survivors from those who died. Thus, reduced overall HRV together with frequent ectopy in the subjects without a known structural heart disease seems to result in altered R-R interval dynamics toward more random behavior. This change in the dynamic pattern of fractal-like HR behavior seems to be associated with an increased risk for cardiac death, independent of the study population.

CONCLUSIONS

The type of editing and the amount of ectopic beats have quantitatively different effects on the dynamic measures of fractal-like R-R interval behavior among the healthy subjects and post-AMI patients. This is mainly due to basic differences in the magnitude of overall and beat-to-beat HRV between these groups. The present analysis also showed that it is not necessary to delete or edit the ectopic beats when fractal analysis of HRV is used for prognostic purposes among healthy subjects or post-AMI patients. In fact, unedited short-term fractal scaling exponent seems to provide more powerful prognostic information than the other HRV indices in general population.

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