Annals of Biomedical Engineering, Vol. 35, No. 2, February 2007 (© 2006) pp. 201–207
DOI: 10.1007/s10439-006-9220-7

Scaling Characteristics of Heart Rate Time Series Before the Onset of Ventricular Tachycardia

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(Received 9 March 2006; accepted 16 October 2006; published online: 14 December 2006)

Abstract—Ventricular tachycardia (VT) provokes sudden cardiac death (SCD), which is a major cause of mortality in developed countries. Implantable cardioverter-defibrillators (ICDs) are an efficient therapy for SCD prevention. In this study we analyze heart rate variability (HRV) in data stored by ICDs.

In 29 patients exhibiting VT episodes, the last 1000 normal beat-to-beat intervals are analyzed and compared to an individually acquired control time series (CON). HRV analysis is performed with standard parameters of time and frequency domain as suggested by the HRV Task Force. For scaling analyses of heart rate time series, the fractal dimension is analysed, applying Higuchi's algorithm (HFD). Furthermore, detrended fluctuation analysis (DFA) is performed.

None of the standard HRV parameters shows significant differences between CON and VT. Before the onset of VT, the scaling characteristics by means of HFD and DFA are significantly changed.

In conclusion, scaling analysis reveals changes in autonomic heart rate modulation preceding VT.

Keywords—Implantable cardioverter defibrillators, Heart rate variability, Fractal dimension, Detrended fluctuation analysis.

INTRODUCTION

Sudden cardiac death (SCD) is a major cause of mortality in the developed countries with an incidence of 3 million cases per year worldwide.[5,9] SCD is usually caused by a malignant tachyarrhythmia. In clinical trials, implantable cardioverter defibrillators (ICDs) have been the most successful therapy for prevention of SCD in high risk patients.[6,26] The detection of ventricular tachycardia (VT) depends on a single ventricular rate sensing signal, a set of programmable detection criteria, and the employed detection algorithm. Modern ICDs offer enhanced detection criteria.[18,29] However, inappropriate defibrillator discharge or antitachycardiac pacing remain an important clinical problem in ICD therapy as they cause unnecessary pain and sometimes proarrhythmic effects.[7,34]

Third generation ICDs are capable of storing the beat-to-beat intervals (BBIs) before VT. Therefore, an assessment of the autonomous nervous system (ANS) by means of heart rate variability (HRV) analysis has become available, opening a completely new perspective on the understanding of arrhythmogenesis on one hand and on the capability to intervene on the other hand. The ANS tone seems to have direct impact on the VT development.[8,16] However, studies analyzing in ICD stored BBI data led to different results.[17,19–23,28,33,36]On the one hand it was discovered that mean heart rate, low frequency power and the low-to-high frequency power ratio all increase before VT. On the other hand no significant HRV changes were found. Discrepancies might be caused by different study designs as well as different methods for HRV analysis.

HRV analysis has been demonstrated to be a potential risk predictor in cardiac patients and is widely performed linearly in the time or frequency domains, as specified by the Task Force of the European Society of Cardiology and the North-American Society of Pacing and Electrophysiology.[30]

Many studies, however, have pointed out the impact of non-linear HRV characteristics. Measures considering those non-linear structures include symbolic dynamics,[2,32] correlation dimension, maximum Lyapunov exponents,[11] mutual information[27] and have shown to be of diagnostic relevance.

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In this paper we investigate the scaling characteristics in heart rate time series by applying detrended fluctuation analysis (DFA)[24] and Higuchi's fractal dimension algorithm (HFD), respectively.[12] Both methods provide different ways to estimate the 'Hurst' scaling exponent of mono-fractal self-affine signals.[10] DFA has been utilized previously to investigate heart rate dynamics[25] and has shown to be useful for diagnostics in patients with cardiac disease.[15] Scale-invariance has been commonly observed over a wide range with a characteristic break at segment sizes of 16 heart beats.[25] Consequently, two scaling exponents, termed α_1 and α_2, are computed in the ranges of 4–16 and 16–64 heart beats, respectively. The analysis of HFD is less common for the investigation of heart rate dynamics. Further, power-law scale-invariance has been observed in the very low frequency band of heart rate dynamics.[30]

Hypothesizing that scaling analyses are able to detect HRV changes before the onset of VT, we conduct a study in patients with ICDs in order to forecast life-threatening arrhythmias.

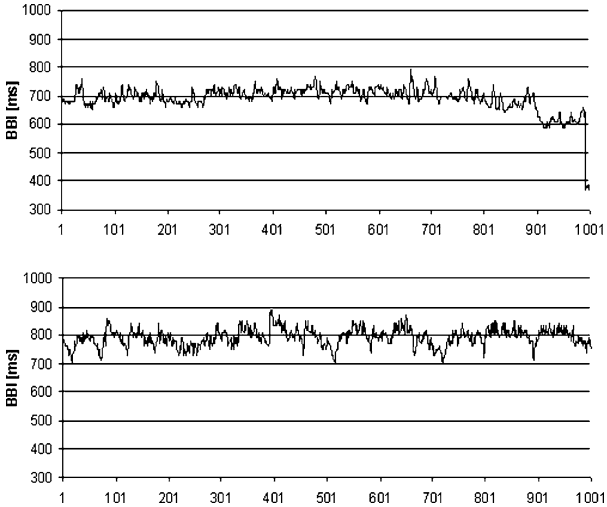

FIGURE 1. Beat-to-beat interval time series stored in an implanted cardioverter defibrillator. Top: Time series before the onset of a ventricular tachyarrhythmia of a patient. The tachyarrhythmia is reflected in the drop of the beat-to-beat intervals at the end of the time series. Bottom: Control beat-to-beat interval time series of the same patient.

METHODS

Data and Preprocessing

Fifty patients with severe congestive heart failure were enrolled at the Franz-Volhard-Hospital Berlin. No patient received a class I or III antiarrhythmic drug prior to the study. All patients had an implanted ICD (PCD 7220/ 7221 Medtronic[14]) capable of storing 1024 BBI before the onset of a VT with a resolution of 10 ms. HRV analysis of a VT time series is performed when there is fewer than 10% of ectopic beats/artifacts ($N = 29$). These results are then compared to individually acquired and arbitrarily selected control time series (CON), without arrhythmic events, that were stored just before a regular ICD follow-up examination (Fig. 1). Artifacts and ectopic beats were removed and interpolated by an algorithm using local variance estimation.[35]

Higuchi's Fractal Dimension

To compute the fractal dimension of a graph, Higuchi[12] considers a finite set of observations $X(j), j = 1, 2, ..., N$ taken at a regular interval k, and evaluates the length $L_m(k)$ of the corresponding graph for different interval lengths k from sequences $X_m{}^k$: $X(m)$, $X(m + k)$, $X(m+2k), \ldots, X(m+[(N-m)/k])$, where $m = 1, 2, ..., k$ and $(N - m)/k$ denotes the integer part of $(N-m)/k$. The length of the graph is calculated as:

$$L_m(k) = \left(\sum_{i=1}^{\left[\frac{N-m}{k}\right]} |X(m+ik) - X(m+(i-1)k)| \right) \frac{N-1}{\left[\frac{N-m}{k}\right] k^2}$$

If the behavior of the graph has fractal characteristics over the available range k then

$L(k) \sim k^{-D_f}$, where D_f is the fractal dimension and $L(k)$ is the average value over k partial lengths of the graph. For a straight line, $D_f = 1$. For Brownian motion, $D_f = 1.5$, and for Gaussian white noise, D_f saturates at two. For time series with $1/f^{\beta}$ power spectra, $D_f = (5-\beta)/2$. This relationship is valid for $1 < \beta < 3$. Numerical experiments have shown that time series with the same β can show different D_f values, depending on the phase distribution.[13]

Detrended Fluctuation Analysis

The DFA has been developed to analyze long-range correlations (long-memory dependence) in non-stationary data, where conventional fluctuation analyses such as power spectra and Hurst analysis cannot be reliably used.[25] The method works as follows:

Compute the cumulative sum $c(k) = \sum_{i=1}^{k} [s(k) - \bar{s}]$ of the time series s where $\bar{s}$ is the mean of S (using the concept of Random-Walk-Analysis).

Compute the local trend $c_n(k)$ within boxes of varying sizes n (least square fit).

Compute the root mean square of the detrended time series in dependency on box size n as $F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[c(k) - c_n(k)]^2}$, where N denotes the size of S.

Plot $\log_{10} F(n)$ against $\log_{10} n$.

If the data displays long-range dependence then $F(n) \sim n^{\alpha}$, where α is the scaling exponent. For stationary data with scale-invariant temporal organization, the Fourier power spectrum $S(f)$ is $S(f) \sim f^{-\beta}$, where the scaling exponent β is related to α in the following way: $\beta = 2\alpha - 1$. Values of $0 < \alpha < 0.5$ are associated with anti-correlation (i.e. large and small values of the time series are likely to alternate). For Gaussian white noise $\alpha = 0.5$. Values of $0.5 < \alpha \leq 1$ indicate long-range power-law correlations (i.e. large values of the time series are likely to be followed by large values). Values $1 < \alpha \leq 1.5$ represent stronger long-range correlations that are different from power-law where $\alpha = 1.5$ for Brownian motion.[25]

Standard HRV analysis

For standard HRV analysis of VT and CON time series we calculate a parameter set of time and frequency domain measures according to the HRV Task Force (Table 1). The frequency domain analysis is performed with linear interpolated time series of 500 ms resolution, using Fast Fourier Transform with Blackman-Harris windowing.

Statistics

To compare HRV parameters between CON and VT we compute group means, standard deviations as well as Student's *t*-tests for paired data. Parameters were considered statistically significant if $p < 0.05$. Further, linear correlation coefficients are computed between HFD and DFA scaling exponents as well as one-way analysis of variance (ANOVA) in order to test whether the mean of the three scaling exponents (see results) are statistically different from each other.

To estimate inter-individual discriminative power of all computed HRV parameters, we apply linear discriminant functions. Cross-validation was performed with 10-fold cross validation, i.e. 10 models are build using 90% of the data for each model and 10% for validation.

TABLE 1. Standard heart rate variability parameters and their definitions.

Parameter	Definition
meanNN	Mean of all normal *NN* intervals; in ms
sdNN	Standard deviation of all *NN* intervals; in ms
rmssd	Root mean square of successive *NN* interval differences; in ms
VLF	Power in the very low frequency band (0.003–0.04 Hz); in ms^2
LF	Power in the low frequency band (0.04–0.15 Hz); in ms^2
HF	Power in the high frequency band (0.15–0.4 Hz); in ms^2
LFn	Ratio of LF power to HF plus LF power

RESULTS

Scaling Analysis

Heart rate time series show fractal characteristics, but the scaling behavior cannot be described by a single scaling exponent (see Fig. 2). Despite of computing two fixed scaling exponents as has been proposed for DFA,[25] we follow a more intuitive way, relating the well-known VLF, LF, and HF frequency bands of HRV to the scaling graph (see Table 1). Consequently, three separate scaling exponents are computed.[4] In order to estimate frequency values f_n and f_k from the segment size n and k of DFA and HFD, respectively, in Hertz, the segment sizes are related to the mean heart rate ($meanNN^{-1}$), i.e. $f_n \approx meanNN^{-1}n$ and $f_k \approx meanNN^{-1}k$. Lower and upper boundaries for the analysis are 3 and 64, respectively, as similarly proposed in the original work by

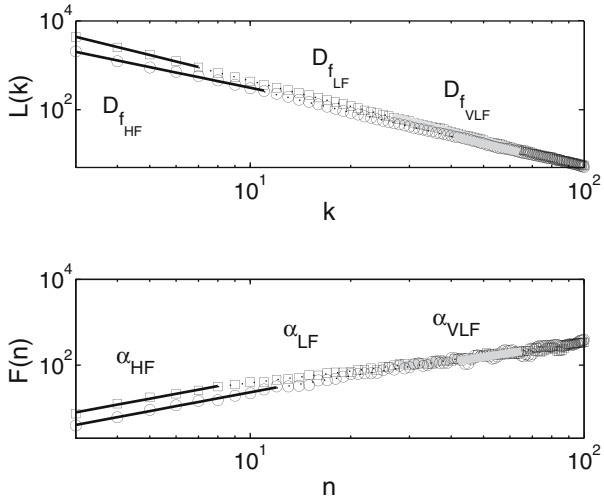

FIGURE 2. Higuchi's fractal dimension analysis (top) and detrended fluctuation analysis (bottom) of one control heart rate time series (squares) and VT time series (circles). For the definitions of *L*(*k*), *k*, *F*(*n*), and *n*, respectively, see text. Black solid line – high frequency (HF) scaling range. Black dotted line – low frequency (LF) scaling range. Gray sold line – very low frequency (VLF) scaling range. Note the different adaptively computed scaling range boundaries for CON and VT are based on mean heart rate, which is different in both recordings.

Peng *et al.*[25] For HFD, all three scaling exponents are significantly different from each other (ANOVA, $p < 0.0001$) in both, the CON and VT time series. For DFA, ANOVA shows significant differences between the three scaling exponents in the CON time series only ($p < 0.02$).

To test whether the scale-invariance, i.e. the fractal relationship, is less pronounced before the onset of VT, we compute the residuals of the VLF, LF, and HF regression lines for HFD and DFA (see Table 2). As a result we do not find significant differences either in HFD or in DFA scaling exponent residuals. The exponents obtained via HFD show significant changes in the HF and LF range, being both decreased before the onset of VT. The scaling exponents obtained via DFA show significant changes in the LF band, only, indicating an increased long-term correlation before the onset of VT.

Linear correlation coefficients between the three calculated HFD and DFA scaling exponents are $r = -0.34$ for the HF range, $r = -0.69$ for the LF range, and $r = -0.57$ for the VLF range, respectively.

TABLE 2. Results of heart rate variability (HRV) analysis presented as means, standard deviations (SD) and paired Student's *t*-test results (*p*).

Parameter	CON		VT		
Standard	Mean	SD	Mean	SD	*p*
mean*NN*	769	142	709	154	0.06
sd*NN*	48	31	43	32	n.s.
rmssd	20	18	16	13	n.s.
VLF	204	307	252	533	n.s.
LF	80	158	86	247	n.s.
HF	29	77	14	24	n.s.
LFn	0.71	0.15	0.68	0.20	n.s.
HFD					
$D_{f_{HF}}$	1.64	0.13	1.58	0.16	0.03
$D_{f_{LF}}$	1.77	0.13	1.70	0.18	0.04
$D_{f_{VLF}}$	1.83	0.21	1.85	0.31	n.s.
$res\_D_{f_{HF}}$	1.49	1.17	1.68	1.41	n.s.
$res\_D_{f_{LF}}$	0.34	0.14	0.36	0.18	n.s.
$res\_D_{f_{VLF}}$	0.23	0.13	0.26	0.21	n.s.
DFA					
α_{HF}	1.26	0.21	1.24	0.28	n.s.
α_{LF}	1.19	0.20	1.28	0.22	0.009
α_{VLF}	1.11	0.19	1.19	0.35	n.s.
res_α_{HF}	3.00	1.22	3.00	1.30	n.s.
res_α_{LF}	1.16	0.35	1.18	0.46	n.s.
res_α_{VLF}	7.57	3.59	6.92	2.61	n.s.

The upper part shows the Task Force standard HRV parameters. The middle part shows the three scaling exponents obtained with Higuchi's fractal dimension algorithm and the residuals of the related regression lines. The lower part shows the three scaling exponents obtained with detrended fluctuation and the residuals of the related regression lines. n.s. – not significant. Residuals were multiplied by 10^3 for clarity.

Standard HRV Analysis

None of the standard HRV parameters are significantly changed before the onset of VT (see Table 2).

Multivariate Statistics

The linear discriminant function comprises of the parameter coefficients as listed in Table 3. The training data results in a missclassification rate of 31% for CON and 28% for VT and consequently an overall missclassification rate of 29%. For the validation data the missclassification for CON is 59% and for VT 41%, resulting in an overall rate of 50%.

DISCUSSION

In this paper we analyze HRV before the onset of VT in order to derive markers for short-term forecasting. In accordance with several other studies, we find no significant changes in the standard HRV parameters.[33,36] However, HRV scaling analyses by means of HFD and DFA reveals significant HRV alterations before the onset of VT. Since the intracardiac electrograms, preceding a VT, were recorded under typical every day conditions, non-stationary signal behavior has to be considered, which invalidates the standard HRV parameters. In contrast, both applied scaling methods are able to cope with those non-stationary features and might therefore be superior for HRV analysis.

HFD analysis reveals three different fractal components of HRV. On larger scales the fractal dimensions increase, i.e. $D_{f_{HF}} < D_{f_{LF}} < D_{f_{VLF}}$. Before the onset of VT, decreased fractal dimensions and therefore decreased complexity of heart rate modulation are found in the HF and LF bands. This might be understood as a general loss of short-term HRV before the

TABLE 3. Standardized coefficients of the linear discriminant analysis function.

HRV parameter	Linear discriminant function coefficients
α_{HF}	4.1859
α_{VLF}	2.2468
$D_{f_{LF}}$	1.4266
$D_{f_{VLF}}$	1.1995
rmssd	0.1616
VLF	0.0026
LF	−0.0029
meanNN	−0.0061
HF	−0.0241
sdNN	−0.0382
α_{LF}	−0.6486
$D_{f_{HF}}$	−8.0120
LFn	−8.0212

onset of VT. The strength of fractal features however, is not affected since the residuals of the regression functions are not significantly altered before VT.

DFA also reveals distinct fractal features of HRV. Correlations decrease in CON on larger scales, i.e. $\alpha_{HF} > \alpha_{LF} > \alpha_{VLF}$. Before the onset of VT, the three regions of scale-invariance are not significantly different from each other, but compared with CON, we find increased correlations in the LF range, which is thought to reflect mainly sympathetic but also vagal influences.[30] This might be interpreted as an increased sympathetic drive, resulting in a stronger mid-range dependence of heart rate modulation and is in accordance with other studies, suggesting increased sympathetic activity as one origin of arrhythmogenesis.[17,19,20,23] Several studies, employing different complexity measures, have found less short-term fluctuations of HRV before the onset of VT, which is seen as a result of decreased vagal activity.[1,36]

Comparing HFD with DFA scaling exponents by means of linear correlation coefficients, it becomes obvious that both methods are not interchangeable for HRV analyses. Thus, HRV cannot be fully explained as a mono-fractal self-affine stochastic process. Both methods should therefore be seen as two complementary approaches for the measurement of scaling features of HRV. Interestingly, the highest agreement ($r = -0.69$) is found in the LF range, where both approaches also revealed significant changes before the onset of VT.

The chosen method of adaptive scaling range computation is based on well-known physiological phenomena, traditionally considered in power spectrum analysis and demonstrating a good fit for all investigated recordings. Even though the three separate scaling exponents might not be fundamentally different in every case, they represent an intuitive, physiologically grounded way to assess the scaling graph and should therefore be always taken into account. Three different scaling ranges have been shown previously, particularly in the HRV of athletes as well as in beat-to-beat blood pressure variability.[3,4]

Multivariate statistics, applying linear discriminate analysis functions, suggest that HRV analysis alone cannot be used to develop a universal predictor for VT and that individual HRV characteristics have to be considered at least. The between-subject variance is bigger than the individual changes before the onset of VT and consequently the classification of the validation data is purely random. Consequently, future studies should reinvestigate the predictive accuracy based on repeated individual measurements; thereby also including possible co-factors such as age, day, time of measurement, clinical diagnosis etc. The individual univariate analysis of parameter changes before the onset of VT in the 29 investigated patients, as

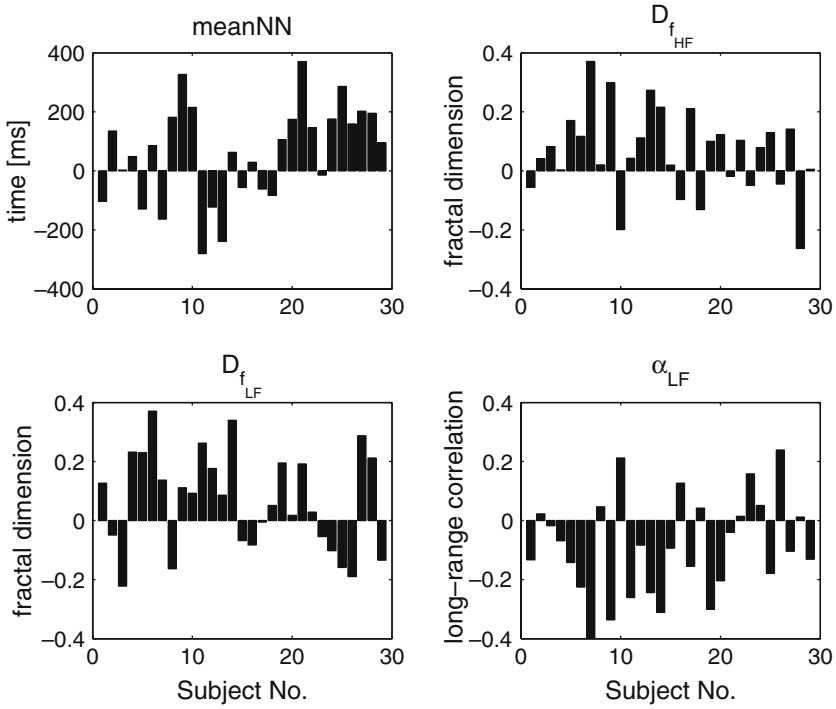

FIGURE 3. Differences in the significantly changed heart rate variability (HRV) parameters meanNN, $D_{f_{HF}}$, $D_{f_{LF}}$, and α_{LF}. The bar plots show the HRV parameter differences between the control measurements and the heart rate time series before the onset of ventricular tachycardia for each of the 29 investigated patients with implantable cardioverter defibrillators.

shown in Fig. 3, raises the question whether short-term forecasting might be possible in a subgroup of patients.

When employing HRV analysis for VT analysis in ICDs, it has to be further considered that only a subgroup of patients with ICDs exhibit a stable sinus rhythm with a limited number of ectopic beats. In our study, we analyze time series with less than 10% of ectopic beats/artifacts to make sure that HRV is not predominantly influenced by post-extrasystolic regulation patterns.[31] Besides ectopic beats, the BBI detection algorithm might also cause artifacts. Consequently, future ICDs performing HRV analysis should necessarily feature a powerful filter algorithm for reliable HRV analysis that minimizes risk of erroneous BBI estimation and avoids inappropriate defibrillator discharges.

In conclusion, the scaling features, particularly in the LF range, are significantly changed before the onset of VT, indicating changes in autonomic heart rate modulation preceding VT.

ACKNOWLEDGMENTS

This study was supported by grants form the Deutsche Forschungsgemeinschaft (DFG Vo505/3-1 and DFG Vo505/4-2) and the Australian Research Council (DP0663345).

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