Forecasting of Life Threatening Arrhythmias Using the Compression Entropy of Heart Rate

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Summary

Objectives: Ventricular tachycardia (VT) provoking sudden cardiac death (SCD) are a major cause of mortality in the developed countries. The most efficient therapy for SCD prevention are implantable cardioverter defibrillators (ICD). In this study heart rate variability (HRV) measures were analyzed for short-term forecasting of VT in order to improve VT sensing and to enable a patient warning of forthcoming shocks.

Methods: The last 1000 normal beat-to-beat intervals before 50 VT episodes stored by the ICD were analyzed and compared to individually acquired control time series (CON). HRV analysis was performed with standard parameters of time and frequency domain as suggested by the HRV Task Force and furthermore with a newly developed and optimized nonlinear parameter that assesses the compression entropy of heart rate (H_c).

Results: Except of meanNN ($p = 0.02$) we found no significant differences in standard HRV parameters. In contrast, H_c revealed highly significant ($p = 0.007$) alterations in VT compared with CON suggesting a decreased complexity before the onset of VT.

Conclusion: Compression entropy might be a suitable parameter for short-term forecasting of life-threatening tachycardia in ICD.

Keywords

Implantable cardioverter defibrillators, heart rate variability, nonlinear dynamics

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1. Introduction

Sudden cardiac death (SCD) is a leading cause of mortality in the developed countries with an incidence of 3 million cases per year worldwide [1, 2]. SCD is usually caused by a malignant tachyarrhythmia. In clinical trials, implantable cardioverter defibrillators (ICD) have been the most successful therapy to prevent SCD in high risk patients [3, 4]. The detection of ventricular tachycardia (VT) depends on a single ventricular rate sensing signal, a set of programmable detection criteria, and the resulting detection algorithm. Modern ICD offer enhanced detection criteria [5, 6]. However, inappropriate shocks or antitachycardiac pacing remain an important clinical problem in the ICD therapy as they cause unnecessary pain and sometimes proarrhythmic effects [7, 8].

Third generation ICD are capable of storing the beat-to-beat intervals (BBI) 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 arrhythmogenesis. The ANS tone seems to have direct impact on the VT development [9, 10]. However, studies analyzing in ICD stored BBI data led to different results [11-19]. On the one hand it was discovered that mean heart rate, low frequency power and the low to high frequency power ratio, respectively, were increased before VT, on the other hand no significant HRV changes were found. The discrepancy is probably caused by a modified study design as well as different methods for HRV analysis.

HRV analysis has demonstrated to be a potential risk predictor in cardiac patients and is widely performed in time and frequency domain specified by the Task Force of the European Society of Cardiology and the North-American Society of Pacing and Electrophysiology [20].

As a novel approach we assessed the complexity of BBI time series based on its compressibility. According to Shannon's information theory there is a limit in encoding a given sequence, its entropy [21]. Benedetto et al. applied zip-coding for entropy estimation in language trees [22]. Hypothesizing that a robust compressibility based entropy measure is suitable to detect HRV changes before the onset of VT we conducted a study in patients with ICD in order to forecast life-threatening arrhythmias.

2. Methods

2.1 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) capable of storing 1024 BBI before the onset of a VT with a resolution of 10 ms. HRV analysis of VT time series was performed in comparison with 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 a local variance estimation [23].

2.2 Data compression

In 1977 Ziv and Lempel [24] developed an universal algorithm for lossless data compression (LZ77) using string-matching on a sliding window that is nowadays implemented in many tools including 'zip' and 'Stacker'. The algorithm is briefly explained here (Fig. 2):

A sequence of symbols $\mathbf{x} = x_1, x_2, \ldots$ of length L from some given alphabet Θ of size $\Theta = |\Theta|$ is to be compressed. Subsequences $(x_m, x_{m+1},\ldots,x_n)$ of $\mathbf{x}$ will be denoted by x_m^n.

The algorithm keeps the w most recently encoded source symbols (sliding window of size w). The not-yet-encoded sequence of symbols is stored in the lookahead buffer of size b. The encoder positioned at p looks for the longest match of length n between the not-yet-encoded n-string x_p^{p+n-1} in the lookahead buffer and the already encoded string $x_{p-w+v}^{p-w+v+n-1}$ in the window beginning at position v. Thus, the matching string of n symbols is simply encoded by encoding the integers n and v, i.e. a pointer to the previous occurrence of this string in the sliding window. In other words, the LZ77 algorithm operates in the following steps:

a) Encode the first w symbols without compression
b) Set the pointer $p = w+1$
c) Find for some v in the range of $1 \le v \le w$ the largest n in the range of $1 \le n \le b$ such that $x_p^{p+n-1} = x_{p-w+v}^{p-w+v+n-1}$
d) Encode the integers n and v into unary-binary code and the symbol $x_{p+n} \in \Theta$ without compression
e) Set the pointer p to $p = n + 1$ and go to step 3 (iterate)

From the point of information theory the smallest algorithm that produces a string is the entropy of that string (Chaitin-Kolmogorov entropy [25, 26]). Although it is theoretically impossible to develop such an algorithm data compression techniques might be a good approximation. Assuming that the source is an ergodic process the entropy per character x is the length of the compressed string divided by the length of the original string if L tends to ∞.

2.3 Compression Entropy of Heart Rate

Utilizing data compression for HRV analysis the source is the sinus node emitting a sequence of BBI. Hence, the alphabet Θ consists of different BBI whereas Φ is mainly affected by the sampling rate s. Consequently, the implementation has to consider integer numbers. Furthermore, a transformation of the BBI string into a unary-binary code is unnecessary for entropy estimation. A matrix $\mathbf{M}$ of length K storing

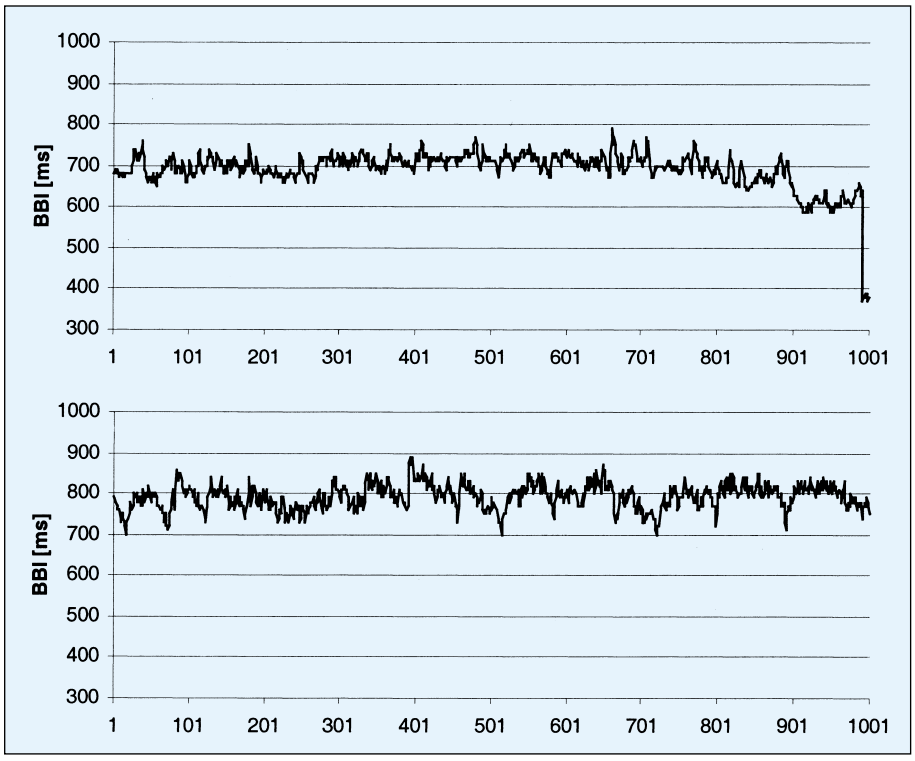

Fig. 1 Beat-to-beat interval time series stored in an implanted cardioverter defibrillator. Top: Time series before the onset of a ventricular tachyarrhythmia of a patient. Bottom: Control time series of the same patient

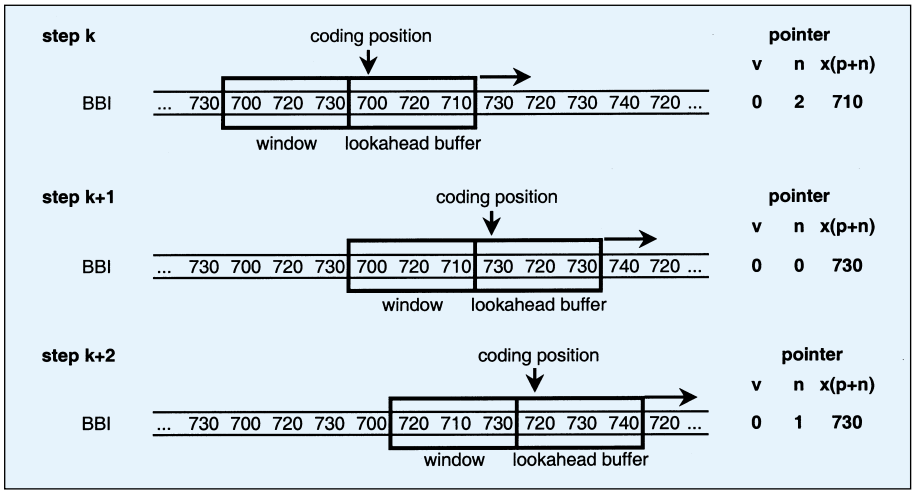

Fig. 2 H_c scheme. Window (size three) and lookahead buffer (size three) are shifted through the stream of BBI. The pointer stores position v, length of the matching string n, and the consecutive BBI x(p + n)

n_k, v_k, and x_{kp+n} for each pointer k contains the information. The compression entropy of heart rate H_c is defined as K divided by L. Considering its influencing variables sampling rate, window size, and lookahead buffer size H_c is precisely denoted as $H_c^{s,w,b}$.

2.4 Standard HRV Parameters

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

2.5 Statistics

In order to optimize $H_c^{s,w,b}$ for VT times series analysis *w* and *b* were stepwise incremented and corresponding statistics including median, interquartil range and signed Wilcoxon rank test were computed. The investigated range was $1 \le w \le 20$ and $1 \le b \le 10$, respectively. To prove whether HRV parameters are able to separate between VT and CON we calculated group median, interquartil range, the relative differences and signed Wilcoxon rank test. Parameters were considered statistically significant if $p < 0.05$. Furthermore, Pearson's correlation coefficients were computed between all significant parameters.

3. Results

3.1 Compression Entropy Depending on Window Size and Lookahead Buffer Size

Figure 3 displays the mean H_c of CON depending on window size and lookahead buffer size. H_c depended in a logarithmic-alike behavior from window size. Although H_c decreased with an increasing lookahead buffer size its influence was noticeable up to a lookahead buffer size of five. The computed H_c values ranged from $H_c^{100,1,1}$: 0.77 (0.68-0.85) to $H_c^{100,20,10}$: 0.39 (0.34-0.49). Group VT showed a similar behavior ranging between $H_c^{100,1,1}$: 0.75 (0.67- 0.82) and $H_c^{100,20,10}$: 0.39 (0.33-0.43).

Figure 4 shows the results of the signed Wilcoxon rank test between CON and VT depending on window and lookahead buffer size. An optimum separation between CON and VT was achieved at a window size of 7 and a lookahead buffer size of 3 ($H_c^{100,7,3}$: 0.48 (0.41-0.61) vs. 0.49 (0.41 to 0.53); $p = 0.007$). Here, the median relative difference of H_c between CON and VT was 8% (Table 2). Significance by chance due to multiple testing is implausible as similar results were achieved within an area of $2 < w < 10$ and $2 < b < 9$.

3.2 Standard HRV Analysis

Table 2 displays the medians of CON and VT, interquartil ranges, relative differences and signed Wilcoxon rank test results of the calculated HRV measures. Except for meanNN (CON: 745 (656-853) vs. VT: 699 (585-802); $p = 0.02$) none of the standard HRV measures was significantly altered before the onset of VT. The correlation coefficient between meanNN and H_c was $r = 0.63$.

Table 1 HRV 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
P	Power in the frequency band (0-0.4 Hz); in ms²
VLF	Power in the very low frequency band (0.003-0.04Hz); in ms²
LF	Power in the low frequency band (0.04-0.15 Hz); in ms²
HF	Power in the high frequency band (0.15-0.4 Hz); in ms²
LF/HF	Ratio of LF power to HF power

4. Discussion

In this paper we introduced a novel method for nonlinear HRV analysis using compression entropy of heart rate. To prove whether HRV analysis provides suitable markers for short-term forecasting of life-threatening arrhythmias in ICD-patients, a set of 50 BBI time series before VT was analyzed. Except for meanNN that was slightly significantly decreased before VT, the analysis revealed no other significantly changed standard HRV parameter, whereas the new H_c parameter was highly significantly reduced before the onset of VT. The reduction of meanNN is in accordance with findings of other authors [11, 19]. As H_c has some correlation ($r = 0.63$) with meanNN we performed a subgroup analysis to prove whether H_c provides additional and partly independent information. Thus, pairs of

data with a meanNN differing more than 200 ms were rejected (40 data pairs remained) and the statistical analysis was repeated subsequently. As a result, the significant difference in meanNN was lost whereas the significance in H_c was preserved ($p = 0.03$) demonstrating the potential contribution of H_c.

The intracardiac electrograms preceding a VT were recorded under daily life conditions. Thus, a non-stationary BBI behavior negatively influencing standard HRV parameters has to be considered. Besides ectopic beats, the BBI detection algorithm of ICD might also cause artifacts. Therefore, the originally acquired BBI time series had to be filtered subsequently. Consequently, future ICD performing HRV analysis should necessarily feature a powerful filter algorithm that minimizes risk of erroneous BBI estimation to avoid inappropriate shocks. However, due to the sliding window technique H_c is relatively insensitive to artifacts and instationarity which have only a locally limited influence to the window and lookahead buffer size.

The variations of lookahead buffer size and window size revealed an optimum separation between VT and CON, i.e. the highest significance, at relatively small sizes ($w = 7, b = 3$). Anyhow, the analyses showed that within a narrow range both parameters might be varied without a major loss of significance (see Fig. 4). Apparently, reduced short-term fluctuations of HRV resulted in an increased compression in VT. This might be in consistence with the findings by Wessel et al. [12] and is supposably caused by the shift of sympathovagal balance toward sympathetic predominance and reduced vagal tone of the ANS [11].

Furthermore, the gradient of H_c in dependency of w and b (Fig. 4) suggests a sensitivity of H_c to vagally rather than sympathetically mediated components of HRV. Since compression entropy analysis represents a short-term method longer lasting patterns reflecting especially sympathetically mediated influences are not or only partially considered for compression.

Besides window size and lookahead buffer size H_c probably depends on the sampling rate and should therefore be a subject of further investigations. Furthermore, a larger data set should be acquired to validate the presented results but also to quantify and classify different mechanisms of arrhythmia development. Future analyses should also investigate the influence of VT cycle length and different arrhythmia substrates on its predictability [13].

In conclusion, the nonlinear parameter H_c revealed significant changes in HRV before the onset of VT and might be suitable

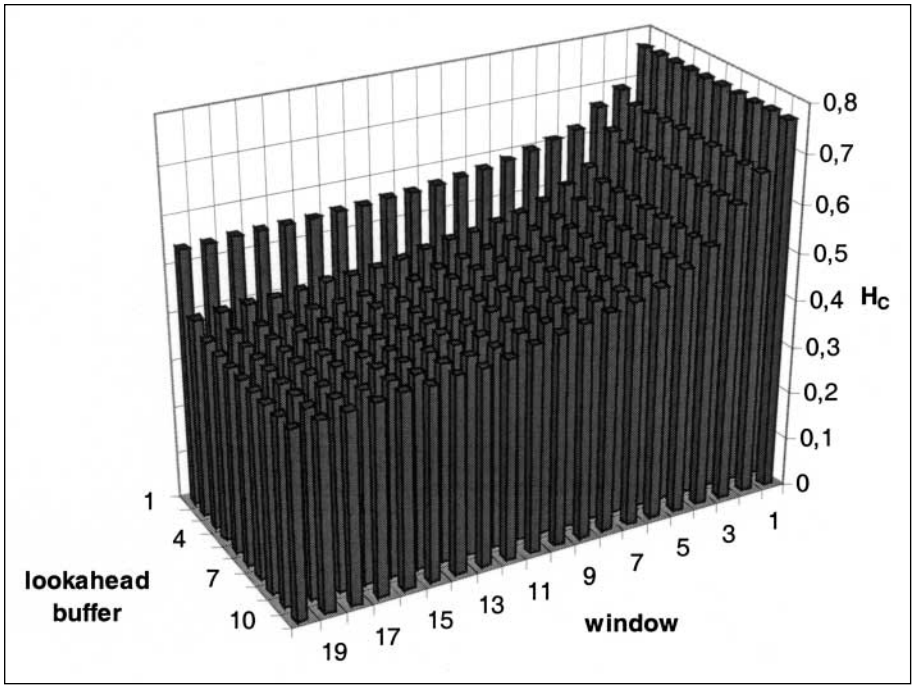

Fig. 3 Compression entropy of heart rate depending on lookahead buffer size and window size. Group mean of CON

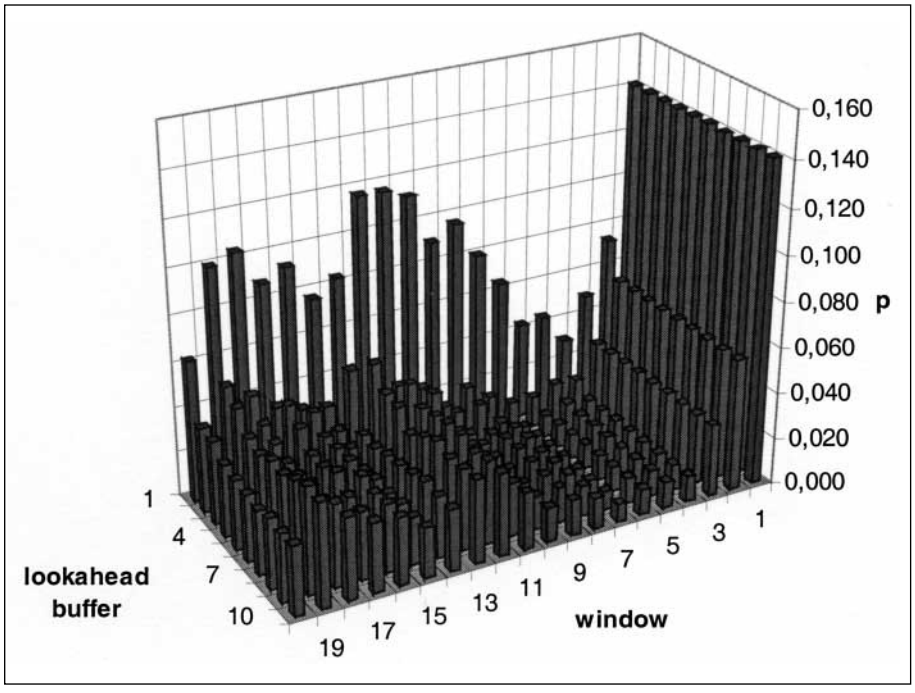

Fig. 4 Wilcoxon test values (VT vs. CON) depending on lookahead buffer size and window size

Table 2 Results of HRV analysis. Median, interquartil range and Wilcoxon test results (n.s. – not significant)

	CON			VT			relative difference [%]			
parameter	median	interquartil range		median	interquartil range		median	interquartil range		p
meanNN [ms]	745	656	853	699	585	802	10	-9,52	22	0.02
sdNN [ms]	50	30	66	38	23	56	7	-32	40	n.s.
rmssd [ms]	17	11	28	15	12	25	12	-20	36	n.s.
P [ms²]	36.1	12.5	132.7	17.7	4.9	114.8	23	-100	80	n.s.
VLF [ms²]	16.1	5.1	52.1	7.0	2.3	71.2	36	-89	70	n.s.
LF [ms²]	4.2	1.4	10.8	3.3	0.5	15.5	30	-33	69	n.s.
HF [ms²]	1.4	0.4	5.2	1.0	0.4	5.2	6	-65	61	n.s.
LF/HF [n.u.]	2.6	1.6	4.1	2.0	1.1	3.2	21	-23	49	n.s.
H_c [n.u.]	0.48	0.42	0.61	0.49	0.41	0.53	8	-6	16	0.007

for the short-term forecasting of life-threatening arrhythmias in ICD in order to improve VT sensing but also to enable an early patient warning of forthcoming shocks.

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