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Heart rate variability before the onset of ventricular tachycardia: differences between slow and fast arrhythmias

Udo Meyerfeldt[a,*], Niels Wessel[b], Henry Schütt[a], Daniela Selbig[a], Agnes Schumann[c], Andreas Voss[c], Jürgen Kurths[b], Christine Ziehmann[b], Rainer Dietz[a], Alexander Schirdewan[a]

[a]*HELIOS Klinikum Berlin, Franz-Volhard-Hospital, Charité, Humboldt-University, Wiltbergstrasse 50, D-13125 Berlin, Germany*

[b]*University of Potsdam, Potsdam, Germany*

[c]*University of Applied Sciences, Jena, Germany*

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Abstract

Background: We tested whether or not heart rate variability (HRV) changes can serve as early signs of ventricular tachycardia (VT) and predict slow and fast VT in patients with an implantable cardioverter defibrillator (ICD). *Methods and results:* We studied the ICD stored 1000 beat-to-beat intervals before the onset of VT (131 episodes) and during a control time without VT (74 series) in 63 chronic heart failure ICD patients. Standard HRV parameters as well as two nonlinear parameters, namely 'Polvar10' from symbolic dynamics and the finite time growth rates 'Fitgra9' were calculated. Comparing the control and the VT series, no linear HRV parameter showed a significant difference. The nonlinear parameters detected a significant increase in short phases with low variability before the onset of VT (for time series with less than 10% ectopy, $P<0.05$). Subdividing VT into fast (cycle length $\leq$270 ms) and slow (>270 ms) events, we found that the onset of slow VT was characterized by a significant increase in heart rate, whereas fast VT was triggered during decreased heart rates, compared to the control series. *Conclusions:* Our data may permit the development of automatic ICD algorithms based on nonlinear dynamic HRV parameters to predict VT before it starts. Furthermore, they may facilitate improved prevention strategies.

Keywords: Autonomic nervous system; Defibrillator; Ventricular tachycardia; Heart rate variability

1. Introduction

Implantable cardioverter defibrillators (ICD) are a safe and effective treatment for ventricular tachycardia (VT) [1–4]. Third generation ICD offer not only important advances in arrhythmia treatment, but also permit the correct characterization of the rhythm leading to intervention [5–7]. This feature has been extremely helpful in systematically investigating the natural history of spontaneous VT. Previous VT studies depended on randomly recorded episodes during Holter monitoring. These studies captured only relatively small numbers of VT episodes from patients with various heart diseases [8–10]. In contrast, ICD studies have examined the electrocardiographic initiating patterns, especially the occurrence of premature beats and special beat sequences [11–17]. These studies were based on short-term intracardiac ICD electrocardiogram storage. Newer ICD systems offer not only a short-term intracardiac electrocardiogram, but also an RR-interval memory up to 1024 consecutive beat-to-beat intervals before

*Corresponding author. Tel.: +49-30-9417-2443; fax: +49-30-9417-2466.

E-mail address: meyerfeldt@fvk-berlin.de (U. Meyerfeldt).

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the start of VT. This feature allows a heart rate variability (HRV) analysis of many spontaneous VT episodes to estimate the influence of the autonomic nervous system on the origin of VT. Autonomic nervous system tone has a significant bearing on VT development [18–24]. The hypothesis of our study was that VT can be predicted by RR-interval analysis. By identification of specific RR-interval trigger patterns, we assumed it may be possible to identify specific VT predictors in patients with an ICD for new preventative strategies. We therefore calculated different linear and nonlinear HRV parameters from ICD stored VT episodes [17,25–28]. A new promising approach for the estimation of autonomic tone, the heart rate turbulence [29], is beyond the scope of our paper—it requires a greater amount of data.

Table 1
Characteristics of the patients (mean±S.D.)

Gender	
Male	55
Female	8
Age (years)	58±12
Range	(42–73)
Heart disease	
CAD	48 (76%)
DCM	11 (18%)
HTN	4 (6%)
LVEF	36±14%
Range	(15–45%)
AA drugs	
Metoprolol	39 (85%)
Class I or II	0
ICD indication	
MVT	56 (79%)
VF	7 (11%)

CAD, coronary heart disease; DCM, dilated cardiomyopathy; HTN, hypertensive heart disease; LVEF, left ventricular ejection fraction; AA, antiarrhythmic drugs; ICD, implantable cardiac defibrillator; MVT, multiple ventricular tachycardias; VF, ventricular fibrillation.

2. Methods

2.1. Patients

We studied the ICD stored beat-to-beat intervals before the onset of 131 VT episodes and at 74 control intervals without VT in 63 ICD patients of the Franz-Volhard-Hospital with severe congestive heart failure. No patient had received a class I or class III antiarrhythmic drug for 18±9 months prior to the study. The patient characteristics are shown in Table 1. The patients underwent implantation of an ICD (PCD 7220/7221, Medtronic) capable of storing at least 1024 beat-to-beat intervals prior to onset of VT (10-ms resolution), which corresponds to about 15 min. We analyzed the time series just before the onset of VT and at an arbitrarily selected control period without an arrhythmic event stored just before a regular ICD follow-up examination. Time series including more than one episode of nonsustained VT, episode of induced VT, ventricular pacing, or more than 10% of ventricular premature beats are excluded from the analysis. To estimate the amount of ventricular premature beats we use an adaptive filtering algorithm for preprocessing, which tends to be superior to standard algorithms [30]. The beat-to-beat intervals of the VT at the end of the time series were removed from the tachograms so that we analyzed only the dynamics occurring immediately prior to VT.

Fig. 1 shows an example of 1000 beat-to-beat intervals prior to a sustained VT as well as a control tachogram from the same patient. To subdivide the VT episodes into slow and fast arrhythmias we used the cut-off point of 270 ms. At this cycle length the efficacy of antitachycardia stimulation is low and the differentiation between monomorphic and polymorphic VT by a stored bipolar or farfield electrocardiogram is not always possible.

2.2. Standard heart rate variability analysis

To detect early signs of life-threatening VT, we applied a multiparametric analysis. Before starting the analysis, ventricular premature beats and artifacts usually should be removed from the time series to construct the so-called ‘normal-to-normal’ beat time series (NN). We used the adaptive filtering algorithm [30] for preprocessing of the data. The following standard HRV parameters from time domain [25] were calculated from all corrected and from the original unfiltered time series: the mean beat-to-beat interval of the time series (meanNN), the standard deviation (sdNN), the percentage of beat-to-beat interval differences greater than 50 ms (pNN50), and the root mean square of successive beat-to-beat interval differences (rmssd). In addition, the standard

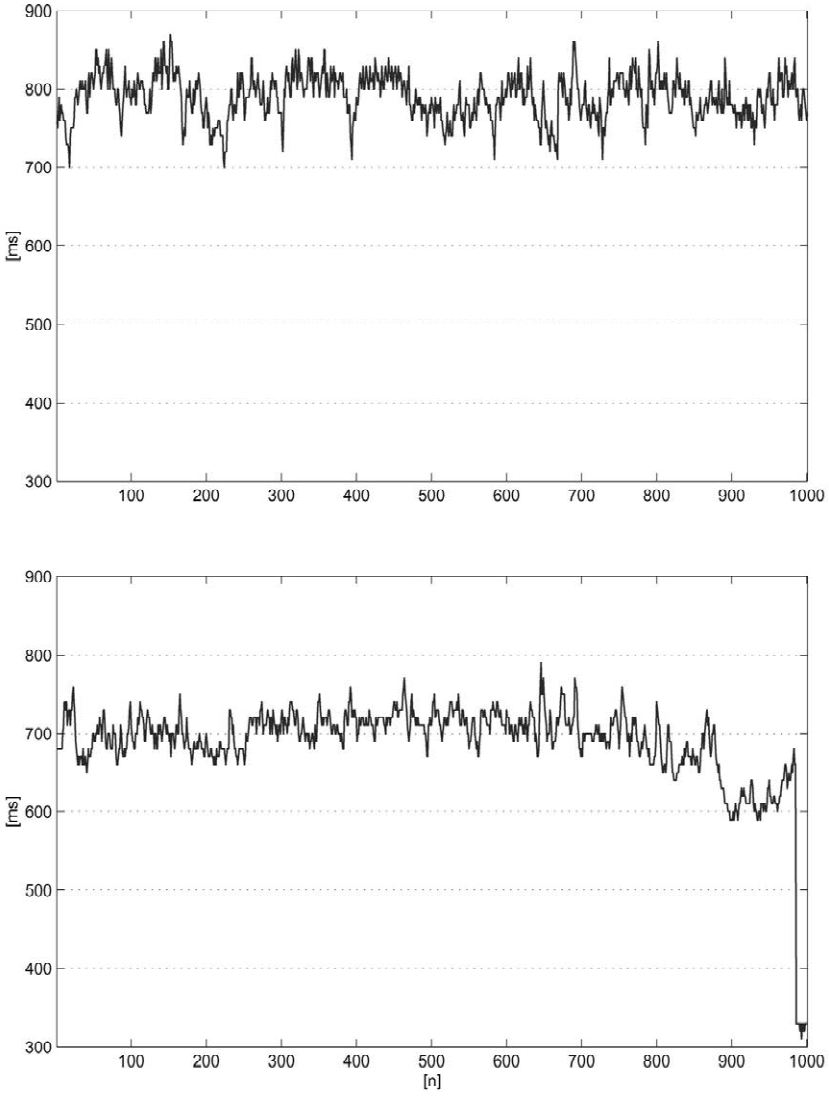

Fig. 1. One thousand beat-to-beat intervals before a sustained VT (below) and the respective control time series (above) from the same patient. For HRV analysis, all beat-to-beat intervals of the VT itself at the end of time series are removed from the tachograms.

parameters (VLF, LF, HF, and P) were calculated from the frequency domain [25]. VLF represents the power in the frequency band from 0.0033 to 0.04 Hz, LF is the power from 0.04 to 0.15 Hz, HF represents the power from 0.15 to 0.4 Hz, and P denotes the total power from 0.0033 to 0.4 Hz. The spectra were estimated using a fast Fourier transformation. To avoid any 'leakage' effect, a Blackman Harris window function was applied. The following ratios were included in the analysis: VLF/P, HF/P, and LF/HF, as well as LFn the normalized low frequency band. These standard parameters of HRV analysis are based on linear techniques. To classify dynamic changes in the time series, we present the following nonlinear concepts of symbolic dynamics and the finite-time growth rates outlined below.

2.3. Symbolic dynamics

Heart rate variability reflects the complex interactions of many different control loops of the cardiovascular system. With regard to the complexity of the sinus node activity modulation system, a more predominantly nonlinear behavior must be assumed. In this way, the detailed description and classification of dynamic changes using time and frequency mea-

sures is often not sufficient. Therefore, we introduced methods derived from symbolic dynamics to distinguish between different states of the autonomic interactions [26,27]. The first step is the transformation of the time series into symbol sequences with symbols from a given alphabet. Some details are lost in this process; however, the advantage is that the coarse dynamic behavior can be analyzed. The parameter used, Polvar10 (**Pro**bability of **l**ow **var**iability, **10** ms difference), characterizes short phases of low variability from successive symbols of a simple alphabet, consisting of only the symbols 0 and 1, where 0 stands for a small difference of less than 10 ms between two successive RR-intervals (10 ms is the resolution of the defibrillators used in this study), and where 1 represent cases when the difference between two successive RR-intervals exceeds this limit, specifically given the time series $x_1, x_2, \ldots, x_N$ one obtains the symbol series s_n

$$s_n = \begin{cases} 1: & |x_n - x_{n-1}| \geq 10\,\text{ms} \\ 0: & |x_n - x_{n-1}| < 10\,\text{ms} \end{cases}$$

Words consisting of the unique symbols all 0 or all 1 were counted. To obtain a statistically robust estimate of the word distribution, we restricted ourselves to the 64 words defined by six consecutive symbols. Polvar10 represents the probability of the word 000000 occurring and thus detects even intermittently decreased HRV. We introduced this parameter with the knowledge that a decreased HRV is a risk marker in cardiac patients [25]. The standard parameters of HRV analysis such as sdNN and rmssd are not able to detect short phases with a decreased HRV.

2.4. Finite time growth rates

A second approach to characterize dynamic behavior is the finite time growth rates which are derived from the concept of Lyapunov exponents [31,32]. For the calculation of the growth rates, the state of the system is reconstructed using delay coordinates [33]. In this space, the actual dynamic behavior can be represented by a point and the time evolution of the system by a trajectory. To analyze the stability or predictability of a current situation over a given duration T, its time evolution is compared with the time evolution of the closest analogous situations found in the past, namely, one searches the nearest neighbor $\bar{X}_k$ of the situation X_k in the reconstructed space and observes how these two trajectories diverge in time [17]. From the original distance of both states and the distance of the evolved states X_k^T and $\bar{X}_k^T$ after T steps, we calculate the finite-time growth rate $\lambda_k^{(n,\tau,T)}$:

$$\lambda_k^{(n,\tau,T)} = \frac{1}{T} \ln \frac{\|X_k^T - \bar{X}_k^T\|}{\|X_k - \bar{X}_k\|}, \quad k = 0, \ldots, N - (n-1)\tau$$

where n is the embedding dimension and τ the delay. This value quantifies the local short-term predictability for each situation or point X_k. If the values are positive, the distances increase with time and the state is unstable. The larger the values, the less predictable is the situation. Negative values reflect highly predictable situations. As we have a value of $\lambda_k^{(n,\tau,T)}$ for each X_k from the original time series we can derive a growth rate time series $\lambda_k^{(n,\tau,T)}$. Averaging over k leads to the average growth rate $\lambda^{(n,\tau,T)}$ which quantifies a global short-term predictability. We determined the rate of growth from the average behavior of the five nearest neighbors to reduce noise effects. The embedding dimension is 9 and the delay time is 1, i.e. a state is defined by nine consecutive values of the time series. The average finite time growth rate for an evolution time $T = 1$ is denoted as Fitgra9 (**Fi**nite **t**ime **g**rowth **ra**tes, dimension **9**). For heart rate time series, this parameter can be interpreted as a measure of regularity. The smaller this value, the larger is the number of epochs with regular or predictable short-term dynamics in the HRV time series indicating a loss of short-term variability.

2.5. Statistical analysis

We calculated the parameters described in the previous sections for both the VT and the control time series and then tested for equality of the averaged values obtained from both groups. The statistical analysis was based on the two-tailed *t*-test as well as the nonparametric Mann–Whitney *U*-test.

3. Results

We observed 131 VT episodes and 74 control series in 63 patients. Sixty-four VT episodes and 27 control series were not included because of atrial

Table 2
Summary of 47 control series compared to 67 VT time series

	Control $n=47$	VT $n=67$	P-value
meanNN filtered	760.81±140.22	694.43±138.09	<0.01
meanNN unfiltered	760.96±139.92	693.92±138.37	<0.01
Ectopy time (s)	68.2±98.1	96.0±129.9	n.s.
Ectopy time (%)	9	14	n.s.
VT cycle length		309.6±52.50	

n.s., not significant, $P \geq 0.05$.

fibrillation, permanent pacing, incessant VT, incomplete storage of episodes, or storage artifacts. The remaining 67 VT episodes and 47 control series from 46 patients comprise the report. The mean VT cycle length was 310±53 ms. Comparing the HRV parameters of all 67 VT and 47 control time series, only the mean sinus rhythm cycle length showed differences, the time series leading to VT had a significantly shorter cycle length (meanNN 694.4±138.1 ms), than the control time series (meanNN 760.8±140.2 ms). The ectopy time, calculated as the sum of the coupling interval and the following pause of all premature beats, did not differ between the VT and control time series. The ectopy time of the VT group was 96.0±129.9 s according to 14% of all 1024 beat-to-beat intervals and 68.2±98.1 s, according to 9% of the control time series ($P > 0.05$). These results are summarized in Table 2.

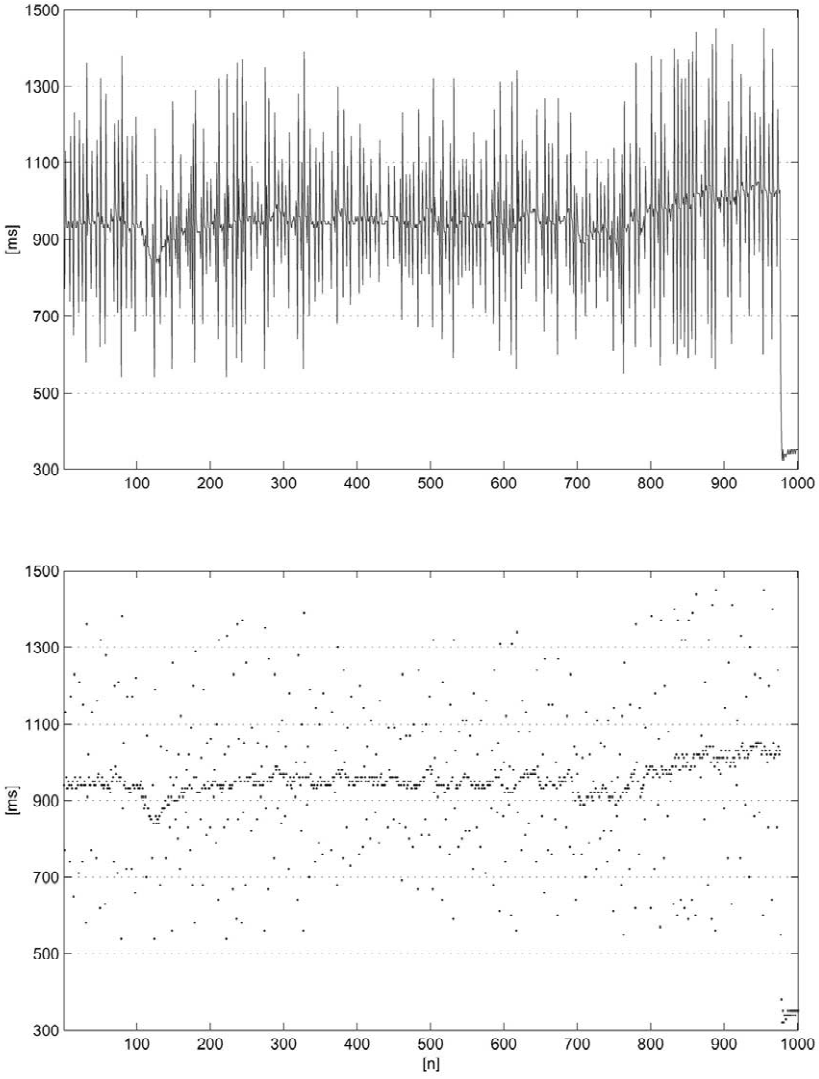

Fig. 2. One thousand beat-to-beat intervals before a VT time series with many ventricular premature beats (above lined, below dotted). When more than 10% ventricular premature beats are present, or when artifacts are abundant, all filtering procedures fail [30]. No useful HRV parameter of the sinus rhythm can be determined in these cases and only the mean heart rate provides a hint of sympathetic activity.

Table 3
The results of 34 control and 36 VT filtered time series, with less than 10% premature beats

	Control $n=34$	VT $n=36$	P-value
meanNN	731.73±122.24	683.32±157.24	n.s.
sdNN	49.00±25.13	49.09±35.83	n.s.
pNN50	0.018±0.022	0.014±0.025	n.s.
rmssd	16.50±8.37	13.74±7.79	n.s.
VLF/P	0.52±0.17	0.54±0.15	n.s.
LH/HF	3.28±1.54	3.93±4.02	n.s.
HF/P	0.04±0.04	0.05±0.04	n.s.
LFn	0.73±0.12	0.72±0.15	n.s.
Polvar10	0.05±0.05	0.13±0.17	<0.05
Fitgra9	0.17±0.06	0.14±0.04	<0.05

n.s., not significant, $P \geq 0.05$.

Recent studies demonstrated the circadian rhythm of HRV, it could be shown that this diurnal rhythm is more marked in the healthy population and in the low risk group than in high-risk patients [34]. The data we analyzed were recorded from a high risk group, therefore, the circadian variations should not have a significant influence in our analysis. All control data sets were stored just before a regular ICD follow up examination in the day time from 08:10 h to 16:48 h, the mean follow-up time was at 11:51 h. The VT events range from 00:02 h to 23:45 h, with the mean time of 12:35 h. More than 64% of all VT episodes occurred in the day time between 08:00 h and 20:00 h. Even though 36% of the tachyarrhythmias happened at night the mean beat-to-beat interval before an VT event was significantly shorter. However, one would expect that at night it would be larger and thus it seems to be that the circadian variation is not relevant in our study.

Since the filter methods in time series with a large number of premature beats are relatively ineffective, as compared in Fig. 2, we calculated the HRV parameters in a second step for 36 VT and 34 control time series with less than 10% of premature beats, as given in Table 3. The difference in the mean cycle length of the VT time series (meanNN 683.3±157.2 ms) and the control time series (meanNN 731.7±122.2 ms) were only apparent as a trend. The other time and frequency domain HRV parameters showed no significant differences between VT and control time series. However, the parameters of nonlinear HRV analysis Polvar10, characterizing short phases of low variability, and Fitgra9, the finite-time growth rates, showed significant differences between VT (Polvar10=0.13±0.17, Fitgra9=0.14±0.04, P-value for Polvar10<0.05) and control (Polvar10=0.05±0.05, Fitgra9=0.17±0.06, P-value for Fitgra9<0.05) time series.

We were next interested if there were RR-interval behavior differences between slow and fast VT and their corresponding control time series. The subdivision was made by the VT cycle length, namely a 270-ms cut-off point. All VT episodes with a cycle length ≤270 ms were defined as potentially fatal VT. We had 48 slow VT episodes with 35 corresponding control time series and 19 fast VT episodes and 17 corresponding control time series. Amongst these time series were 25 slow VT episodes and 21 corresponding control time series as well 11 fast VT time series and their 13 control time series which had <10% premature ventricular beats. These latter time series were used for further analyses. In the filtered time series comparisons, the slow VT were preceded by a significantly shorter sinus rhythm cycle length (665.7±137.8 ms) than their corresponding controls (771.1±154.3 ms, $P<0.01$). The traditional linear HRV parameters of the slow VT time series and their controls did not show significant differences (except meanNN, see Table 4). However, the nonlinear parameters Polvar10 and Fitgra9 revealed significant differences as shown in Table 4.

The fast VT episodes were preceded by an increased sinus rhythm cycle length (828.0±169.4 ms), compared to the control time series (650.9±136.1). However, the HRV analysis did not indicate any significant difference. The nonlinear parameters

Table 4
Filtered time series of VT cycle length >270 ms and their controls with less than 10% ventricular premature beats

	Control $n=21$	VT $n=25$	P-value
meanNN	771.35±154.30	665.68±137.81	<0.01
sdNN	57.13±34.19	49.39±37.47	n.s.
pNN50	0.04±0.11	0.01±0.03	n.s.
rmssd	21.18±21.51	12.98±9.22	n.s.
VLF/P	0.30±0.24	0.26±0.21	n.s.
LH/HF	3.45±1.37	3.94±4.27	n.s.
HF/P	0.05±0.05	0.05±0.04	n.s.
LFn	0.76±0.06	0.73±0.13	n.s.
Polvar10	0.04±0.05	0.13±0.18	<0.05
Fitgra9	0.16±0.06	0.13±0.04	<0.05

n.s., not significant, $P \geq 0.05$.

Table 5
Comparison of filtered VT time series ≤270 ms cycle length and >270 ms cycle length; 25 series with VT>270 ms versus 11 VT series with ≤270 ms

	VT CL>270 ms $n=25$	VT CL≤270 ms $n=11$	P-value
meanNN	665.68±137.81	828.04±169.44	<0.05
sdNN	49.39±37.47	73.62±50.91	n.s.
pNN50	0.01±0.03	0.05±0.04	<0.05
rmssd	12.98±9.22	22.56±11.80	<0.05
VLF/P	0.26±0.21	0.55±0.08	n.s.
LH/HF	3.94±4.27	4.90±2.80	n.s.
HF/P	0.05±0.04	0.04±0.03	n.s.
LFn	0.73±0.13	0.78±0.14	n.s.
Polvar10	0.13±0.18	0.08±0.18	<0.05
Fitgra9	0.13±0.04	0.13±0.03	n.s.

n.s., not significant $P \geq 0.05$.

Polvar10 and Fitgra9 had similar numeric differences as the fast VT time series. The small group sizes were likely responsible for the failure to identify statistical significance.

The contrast between slow and fast VT time series becomes more clear by a direct comparison as shown in Table 5. Whereas the slow VT episodes were preceded by an increase in heart rate indicated by the shorter cycle length (665.7±137.8 ms), the fast VT episodes were triggered during significant slower heart rates (828.0±169.4 ms, $P<0.05$). Fig. 3 shows the 1-min-averaged beat-to-beat intervals before the onset of VT for both groups. The averaged beat-to-beat interval for the slow VT group decreases 2 min

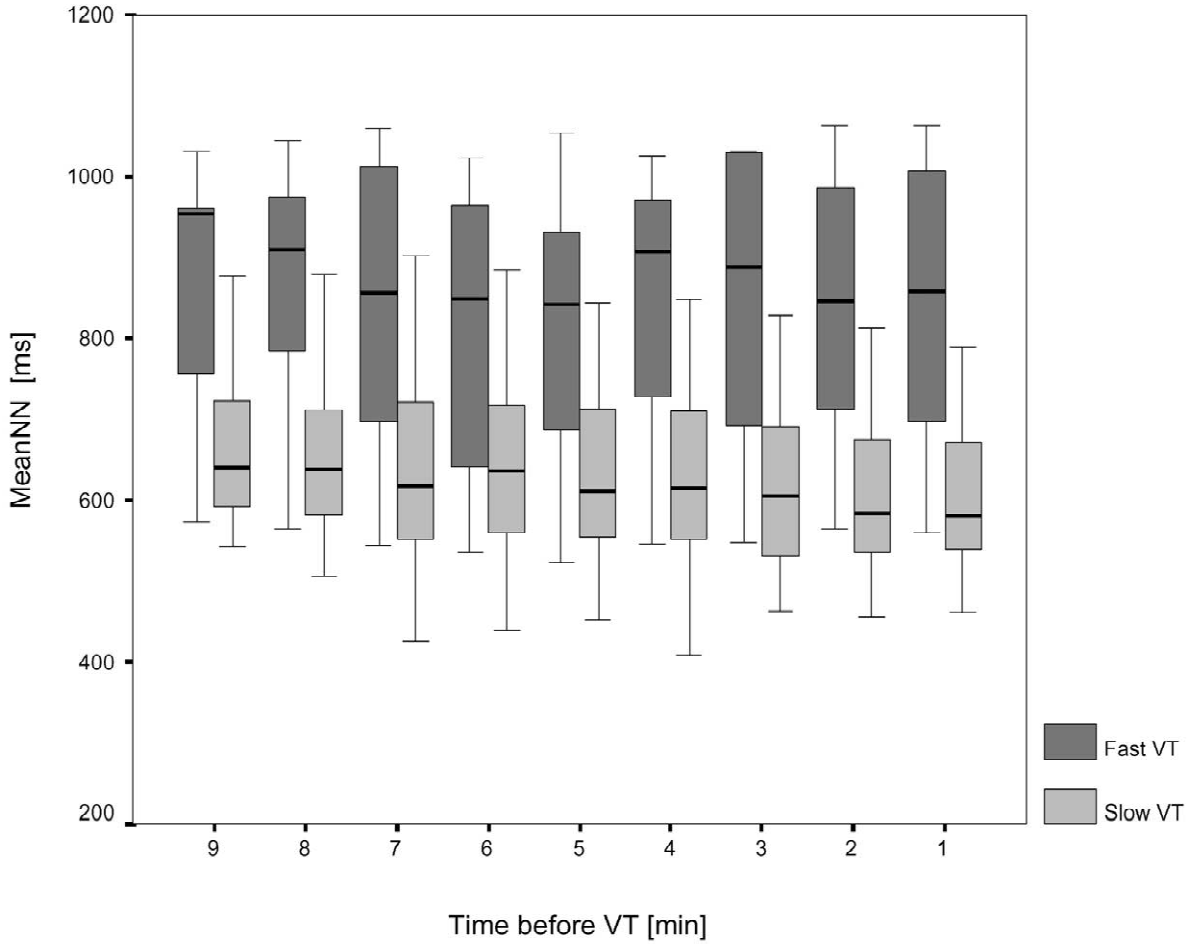

Fig. 3. The averaged 1-min beat-to-beat intervals for the slow and the fast VT group. The values of the fast VT group are significantly higher compared to the beat-to-beat intervals in the slow VT group. Moreover, there is a clear trend for an increase in heart rate from minute 9 to 1 in the slow VT group.

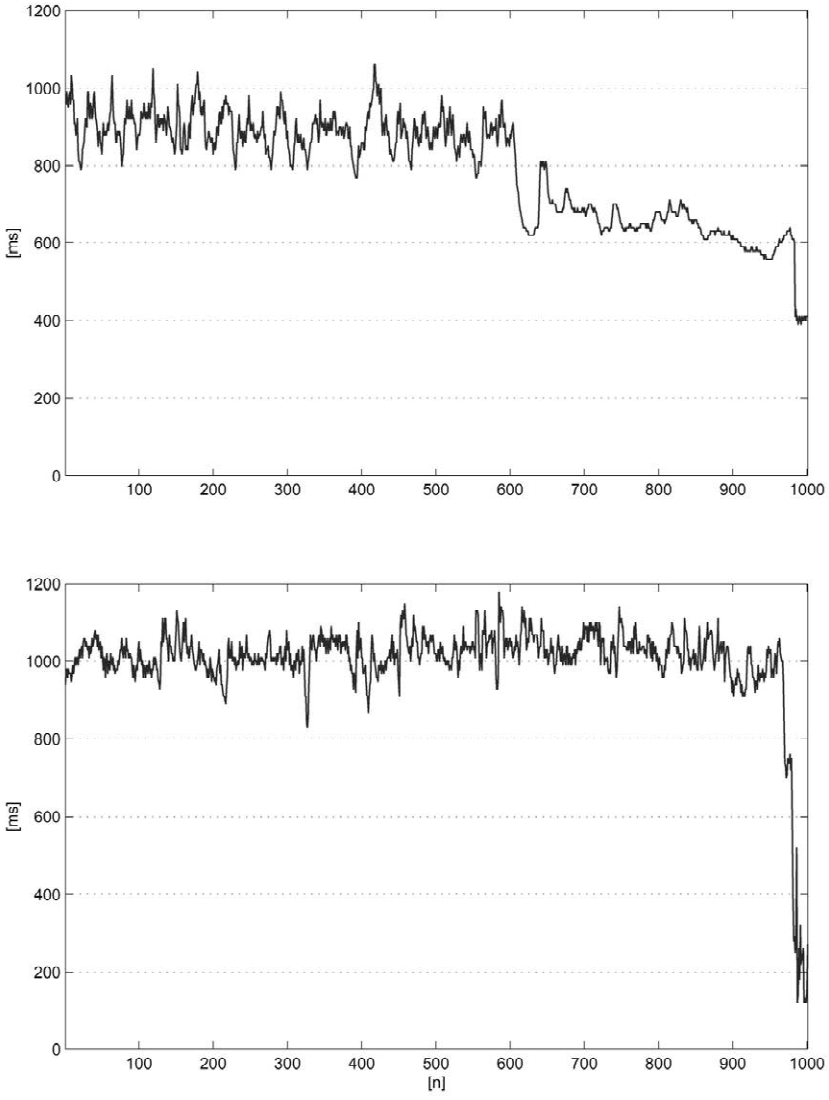

Fig. 4. Two representative VT episodes. The upper time series shows the development to a slow VT. The heart rate increased and the HRV decreased. In contrast, the lower time series demonstrates the evolution to a fast and potentially fatal VT. No changes in heart rate are visible before the onset of VT.

before the onset of VT whereas it remains constant on a higher level for the fast VT group. There were also significant differences in other HRV parameter analysis detected by the pNN50, rmssd and Polvar10 ($P<0.05$). Fig. 4 demonstrates the basic principle. The slow VT develops from a sinus arrhythmia while the fast VT shows no heart rate increase prior to onset.

Beside the circadian rhythm of HRV there is also a circadian pattern of ventricular tachyarrhythmias. The incidence of VT is higher in the morning hours and the afternoon than in the sleeping time at night [35,36]. Our data confirm these results, however, we could not find a difference in diurnal variation between the slow and the fast VTs. The slow VTs occurred between 00:02 h and 23:45 h with a mean time of 12:37 h, whereas the fast VTs happened between 02:12 h and 21:23 h with a mean time of 12:30 h. The percentage of daytime VTs (from 08:00 h to 20:00 h) was 62% in the slow and 69% in the fast VT group. Since we have more fast VTs in the day time we would expect to have a higher heart rate before such events. However, as shown in Table 5, the mean heart rate is significantly slower in the fast

VT group. Thus, it seems to be that the differences found between the slow and the fast VT group were not due to circadian variation of VT occurrence.

Finally, to validate the results obtained above we carried out a validation paired statistical analysis, which considered only one VT and the respective control series. The results in Table 2 were confirmed; the differences in mean heart rate remained significant ($P<0.05$). The same proved true for the data in Table 3; the significant differences for Polvar10 increased to $P=0.03$. The P-value for Fitgra9 was 0.05. Comparing slow VT episodes and their controls given in Table 4, the significant differences for meanNN, Polvar10, and Fitgra9 were confirmed as trends ($P=0.07$, $P=0.06$, and $P=0.10$, respectively). When we compared the VT and the control series of fast VT, no significant differences were found (not shown here). From Table 5, only the significant differences in meanNN were confirmed as a trend ($P=0.06$).

4. Discussion

We identified significant differences in the dynamic behavior of beat-to-beat intervals between the VT and control time series by means of nonlinear dynamics. The parameters Polvar10 and Fitgra9 reflect increased short phases with low variability in patients with congestive heart failure. This result demonstrates that a loss of short-term variability precedes the onset of VT [17]. Similar findings were reported by Mäkikallio and Skinner, who estimated other parameters of nonlinear dynamics during Holter monitoring in post myocardial infarction patients [10,37]. In accord with other authors reporting HRV analyses before VT during Holter monitoring [8–10,38–42] and from ICD stored episodes [20], we could not find significant differences in time or frequency domain parameters in our HRV analyses. The increase in heart rate before the start of the VT described by Nemec et al. [20], Pruvot et al. [43] and Lombardi et al. [44] was confirmed in our data set (Table 2).

It is well known that there is a circadian rhythm of HRV [34]. Since all control data sets were stored in the day time, the VT events however are distributed over the whole day, one might expect an important bias. However, we could show that there is seemingly no influence from circadian variation of HRV.

Another important finding in our study was the significant RR-interval difference before the onset of slow and fast VT. The onset of slow VT was characterized by a significant increase in heart rate, compared to the corresponding control time series. By estimating the linear HRV parameters, there were no differences between the slow VT and control time series. However, by the methods of nonlinear HRV analysis with the Polvar10 and the Fitgra9, we were able to identify significant differences in the data sets. In contrast, the time series before fast VT showed a different behavior. The fast VT episodes were triggered during decreased heart rates, compared to the control time series. This finding was not significant; however, it was a recognizable trend. The standard HRV parameters also showed no significant differences. The nonlinear parameters had the same results as the slow VT results, but the differences were not significant because of the small group sizes. The opposing effects of the autonomic nervous system prior to fast and slow VT episodes were more evident by the direct comparison of the triggering time series. There were significant differences prior to VT as well in the standard parameters meanNN, pNN50 and rmssd as in the nonlinear parameter Polvar10.

In our study, we could confirm the circadian pattern of ventricular tachyarrhythmias. The incidence of VT is higher during the day time than at night [35,36]. However, we did not find a difference in diurnal variation between the slow and the fast VTs. Thus, it seems to be that the above differences were not due to circadian variation of VT occurrence.

We assume that these differences illustrate a different role of autonomic regulation prior to the start of VT in both groups. Therefore, various types of ventricular arrhythmias with a different risk for sudden death may have been triggered during significantly different activation states of the sympathetic and vagal nervous systems. Whereas slow VT began during sympathetic activation, as identified by significantly increased heart rate and decreased linear parameters of heart variability prior to VT, the fast arrhythmias were preceded by decreased heart rates. Both types of arrhythmias were triggered during periods with increased short phases with low variability. This result suggests that the myocardium

becomes susceptible to VT by a more complex mechanism dependent on variable neurohumoral regulatory systems, rather than solely by sympathetic activation. Additional time-dependent modulating factors seem to be involved in arrhythmogenesis, particularly in the case of fast VT. Considering these results, we noticed that all patients received the currently available best medical therapy, especially with the high percentage of beta blockers and ACE inhibitors employed in our study. There were no differences in medical therapy between patients with fast and slow VT. Despite the favorable effects of beta blockers on heart rate variability [45,46] it was nonetheless possible to identify the periods preceding life-threatening VT in a high risk patient group by the described methods of nonlinear dynamics. Moreover, our study demonstrated the advantage of using methods from nonlinear dynamics. Particularly, the evolution of points in phase space provided a deeper insight into the dynamic aspects of rhythm regulation. The limitations of our study were the relatively small number of time series and the subsequently limited statistical analysis in terms of subdivisions concerning age, sex, and heart disease. Thus, these results must be validated with a larger data base. The first studies are now in progress to prevent VT by atrioventricular stimulation to shorten the pause after premature beats [47]. Moreover, heart rate dynamics prior to VT onset in terms of drug treatment are currently being investigated [43]. Our data offer the possibility of developing automatic ICD algorithms based on nonlinear dynamic HRV parameters. This approach may permit the automatic short-term prediction of VT and the initiation of earlier modes of prevention.

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References

[1] Mirowski M, Reid PR, Mower MM et al. Termination of malignant ventricular tachyarrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322–4.

[2] Grimm W, Flores BT, Marchlinski FE. Shock occurrence and survival in 241 patients with implantable cardioverter-defibrillator therapy. Circulation 1993;87:18880–8.

[3] Saksena S. (for the PCD Investigator Group). Clinical outcome of patients with malignant ventricular tachyarrhythmias and a multiprogrammable implantable cardioverter-defibrillator implanted with or without thoracotomy: An international multicenter study. J Am Coll Cardiol 1994;23:1521–30.

[4] The antiarrhythmic versus implantable defibrillators (AVID) investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near fatal ventricular arrhythmias. N Engl J Med 1997;337:1576–83.

[5] Marchlinski FE, Callans DJ, Gottlieb CD et al. Benefits and lessons from stored electrogram information in implantable defibrillators. J Cardiovasc Electrophysiol 1995;6:832–51.

[6] Hook BG, Callans DJ, Kleiman RB et al. Implantable cardioverter-defibrillator therapy in the absence of significant symptoms. Circulation 1993;87:1897–906.

[7] Gronefeld GC, Mauss O, Li YG et al. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. J Cardiovasc Electrophysiol 2000;11:1208–14.

[8] Leclercq JF, Coumel P. Lessons from recordings of sudden death by Holter monitoring. In: de Luna AB et al., editor, Sudden cardiac death, Norwell, MA: Kluwer, 1991, pp. 99–111.

[9] Makikallio TH, Koistinen J, Jordaens L et al. Heart Rate Dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts. Am J Cardiol 1999;83:880–4.

[10] Berger MD, Waxman HL, Buxton AE et al. Spontaneous compared with induced onset of ventricular tachycardia. Circulation 1988;78P:885–92.

[11] Marchlinski FE, Schwartzman D, Gottlieb CD et al. Electrical events associated with arrhythmia initiation and stimulation techniques for arrhythmia prevention. In: Zipes DP, Jalife J, editors, Cardiac electrophysiology: from cell to bedside, 2nd ed., Philadelphia, PA: W.B. Saunders, 1995, pp. 863–77.

[12] Roelke M, Garan H, McGovern BA et al. Analysis of the initiation of spontaneous monomorphic ventricular tachycardia by stored intracardiac electrograms. J Am Coll Cardiol 1994;23:117–22.

[13] Meyerfeldt U, Schirdewan A, Wiedemann M et al. The mode of onset of ventricular tachycardia. A patient-specific phenomenon. Eur Heart J 1997;18:1956–65.

[14] Leenhardt A, Maison-Blanche P, Denjoy I et al. Mechanisms of spontaneous initiation of tachycardias. Arch Mal Coeur Vaiss 1999;92:17–22.

[15] Capucci A, Villani GQ, Groppi F et al. Comparison of therapy detection times between implantable cardioverter defibrillators with standard dual- and single-chamber pacing. J Interv Card Electrophysiol 1999;3:329–33.

[16] Saeed M, Link MS, Mahapatra S et al. Analysis at intracardiac electrograms showing monomorphic ventricular tachycardia in patients with implantable defibrillators. Am J Cardiol 2000;85:580–7.

[17] Wessel N, Ziehmann C, Kurths J et al. Short-term forecasting of life-threatening cardiac arrhythmias based on symbolic dynamics and finite-time growth rates. Phys Rev E 2000;61:733–9.

[18] Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Circulation 1992;85:I77–91.

[19] Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Structure, function and time dependence of risk. Circulation 1992;85:I2–I10.

[20] Nemec J, Hammill SC, Shen WK. Increase in heart rates precedes episodes of ventricular tachycardia and ventricular fibrillation in

patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1999;22:1729–38.
[21] Mani V, Wu X, Wood M et al. Variation of power immediately prior to spontaneous onset of ventricular fibrillation in patients with implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 1999;10:1586–96.
[22] Schubert B, Van Dongen AM, Kirsch GE et al. Beta-adrenergic inhibition of cardiac sodium channels by dual G-protein pathways. Science 1989;245:516–9.
[23] Taylor E, Berger R, Hummel JD et al. Analysis of the pattern of initiation of sustained ventricular arrhythmias in patients with implantable defibrillators. J Cardiovasc Electrophysiol 2000;11:719–26.
[24] Wood MA, Ellenbogen KA. Initiation of spontaneous ventricular tachycardia: from spark to fire. J Cardiovasc Electrophysiol 2000;11:727–9.
[25] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.
[26] Kurths J, Voss A, Witt A et al. Quantitative analysis of heart rate variability. Chaos 1995;5:88–94.
[27] Glass L. Chaos and heart rate variability. J Cardiovasc Electrophysiol 1999;10:1358–60.
[28] Voss A, Kurths J, Kleiner HJ et al. The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. Cardiovasc Res 1996;31:419–33.
[29] Schmidt G, Malik M, Barthel P et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353(9162):1390–6.
[30] Wessel N, Voss A, Malberg H et al. Nonlinear analysis of complex phenomena in cardiological data. Herzschr Elektrophys 2000;11(3):159–73.
[31] Oseledec VI. A multiplicative ergodic theorem. Ljapunov characteristic numbers for dynamical systems. Trans Moscow Math Soc 1968;19:197–231.
[32] Wolf A, Swift JB, Swinney HL et al. Determining Lyapunov Exponents from a time series. Physica D 1985;16:285–317.
[33] Takens F. Detecting strange attractors in turbulence, In: Rand E, Young LS, editors. Dynamical systems and turbulence (Warwick, 1980) (Lecture Notes in Mathematics 898), Berlin: Springer, 1981, pp. 366–381.
[34] Malik M, Farrell T, Camm AJ. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. Am J Cardiol 1990;66:1049–54.
[35] Saito K, Matsuyama K, Niki T et al. Characteristics of non-sustained ventricular tachycardia detected by ambulatory electrocardiography. Jpn Circ J 1984;48:421–6.
[36] Behrens S, Galecka M, Bruggemann T et al. Circadian variation of sustained ventricular tachyarrhythmias terminated by appropriate shocks in patients with an implantable cardioverter defibrillator. Am Heart J 1995;130:79–84.
[37] Skinner JE, Pratt CM, Vybiral T. A reduction in the correlation dimension of heart beat intervals precedes imminent ventricular arrhythmias. Am Heart J 1993;125:731–43.
[38] Denes P, Gabster A, Huang SK. Clinical electrocardiographic and follow-up observations in patients having ventricular fibrillation during Holter monitoring. Role of quinidine therapy. Am J Cardiol 1981;48:9–16.
[39] Huikuri HV, Valkama JO, Airaksinen KE et al. Frequency domain measures of heart variability before the onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. Circulation 1993;87:1220–8.
[40] Shusterman V, Aysin B, Gottipaty V et al. Autonomic nervous system activity and the spontaneous initiation of ventricular tachycardia. ESVEM Investigators. Electrophysiologic Study Versus Electrocardiographic Monitoring Trial. J Am Coll Cardiol 1998;32:1891–9.
[41] Huikuri HV, Seppanen T, Koistinen MJ et al. Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. Circulation 1996;93:1836–44.
[42] Vybiral T, Glaeser DH, Goldberger AL et al. Conventional heart rate variability analysis of ambulatory electrocardiographic recordings fails to predict imminent ventricular fibrillation. J Am Coll Cardiol 1993;22:557–65.
[43] Pruvot E, Thonet G, Vesin JM et al. Heart rate dynamics at the onset of ventricular tachyarrhythmias as retrieved from implantable cardioverter-defibrillators in patients with coronary artery disease. Circulation 2000;101:2398–404.
[44] Lombardi F, Porta A, Marzegalli M et al. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. Am J Cardiol 2000;86:959–63.
[45] Lin JL, Chan HL, Du CC et al. Long-term beta-blocker therapy improves autonomic nervous regulation in advanced congestive heart failure: a longitudinal heart rate variability study. Am Heart J 1999;137:658–865.
[46] Pousset F, Copie X, Lechat P et al. Effects of bisoprolol on heart rate variability in heart failure. Am J Cardiol 1996;77:612–7.
[47] Fromer M, Wietholt D. Algorithm for the prevention of ventricular tachycardia onset: The Prevent Study. Am J Cardiol 1999;83:45D–7D.