Med Biol Eng Comput
DOI 10.1007/s11517-008-0326-y

ORIGINAL ARTICLE

Ventricular arrhythmias and changes in heart rate preceding ventricular tachycardia in patients with an implantable cardioverter defibrillator

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Received: 19 November 2007 / Accepted: 19 February 2008

Abstract The objective was to determine the characteristics of heart rate variability and ventricular arrhythmias prior to the onset of ventricular tachycardia (VT) in patients with an implantable cardioverter defibrillator (ICD). Sixty-eight beat-to-beat time series from 13 patients with an ICD were analyzed to quantify heart rate variability and ventricular arrhythmias. The episodes of VT were classified in one of two groups depending on whether the sinus rate in the 1 min preceding the VT was greater or less than 90 beats per minute. In a subset of patients, increased heart rate and reduced heart rate variability was often observed up to 20 min prior to the VT. There was a non-significant trend to higher incidence of premature ventricular complexes (PVCs) before VT compared to control recordings. The patterns of the ventricular arrhythmias were highly heterogeneous among different patients and even within the same patient. Analysis of the changes of heart rate and heart rate variability may have predictive value about the onset of VT in selected patients. The patterns of ventricular arrhythmia could not be used to predict onset of VT in this group of patients.

Keywords Ventricular arrhythmias · Heart rate variability · Implantable cardioverter defibrillators · Non-linear methods · Ventricular tachycardia

Abbreviations

ACE	Angiotensin converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
CI	Coupling interval
FFT	Fast Fourier transform
FWShannon	Shannon entropy of the symbolic word distribution
HF	Mean power at the high frequency band (from 0.15 to 0.4 Hz)
HRV	Heart rate variability
ICD	Implantable cardioverter defibrillator
LF	Mean power at the low frequency band (from 0.04 to 0.15 Hz)
N	Normal heart beat
NIB	Number of intervening sinus beats (*N*) between two consecutive V beats
NN	RR intervals from normal heartbeats
nu	Normalized units
NYHA	New York Heart Association
pNN50	Percentage of beat-to-beat differences greater than 50 ms
Polvar10	Incidence of beats segments during which the beat-to-beat differences of RR intervals is less than 10 ms

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PVCs	Premature ventricular complexes
RMSsd	Root mean square of successive beat-to-beat differences
sdNN	Standard deviation of NN
TOCSY	Toolbox for Complex Systems
V	Premature ventricular complex
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VTCI	Ventricular tachycardia coupling interval

1 Introduction

Sudden death due to cardiac ventricular arrhythmias is one of the leading causes of death in most developed countries. The implantable cardioverter defibrillator (ICD) automatically detects ventricular tachycardia (VT) or ventricular fibrillation (VF) and provides appropriate therapy, either antitachycardia pacing or a defibrillating shock to terminate the arrhythmia. ICDs are recommended for patients with documented cardiac arrest, low ejection fraction, or genetic abnormalities associated with a high incidence of sudden cardiac death [6, 13, 32, 33]. However, the identification of patients at risk, particularly among the general population, remains a challenge [3, 14].

In addition to their primary clinical role to reduce the incidence of sudden cardiac death, data that were recorded in ICDs and subsequently downloaded have also been used to analyze the conditions that precede the onset of VT and VF [5, 8–11, 20, 25, 28, 30, 31, 34, 37, 39, 43, 46]. The data derived from ICDs complement data from other sources that have analyzed heart rate variability (HRV) [8, 17, 19, 28, 36, 48, 49, 51], premature ventricular complexes (PVCs) [1, 4, 7, 15, 26, 40, 41, 44], and T-wave alternans [18, 23, 35, 38] in assessment of factors that lead to the initiation of ventricular tachycardia and confer an increased risk for sudden cardiac death. Many factors including increased heart rate [16, 19, 20, 24, 27, 31, 34], reduced HRV [11, 17, 19, 22, 28, 30, 31, 36, 43, 45, 48, 49], increased incidence of PVCs [4, 7, 16, 40, 44], and T-wave alternans [18, 35, 38] are associated with an increased risk of sudden cardiac death. However, statistically significant results in clinical studies do not give a clear insight into the mechanisms of arrhythmias in individual patients.

Recent studies have proposed that a new data analysis method, called the "heartprint" may be useful to assess the risk for sudden cardiac death in selected patients based on Holter tape recordings in patients who experienced sudden cardiac death [26, 42]. In contrast to other methods of risk prediction, in selected patients, the heartprint is able to give important information about the mechanism of the arrhythmia. In particular, we have proposed that the heartprint has distinctive features in patients with parasystole and long QT syndrome [26]. However, this earlier study left open many questions. In particular, it is necessary to determine: (1) if other subsets of patients at high risk of sudden cardiac death would also display the same patterns in the heartprints observed in Lerma et al. [26]; (2) if shorter recordings such as those that can be recorded with an ICD contain enough data to construct a meaningful heartprint; and (3) if the heartprint can be used in combination with other methods of risk stratification involving heart rate variability to assess better the mechanisms of sudden cardiac death.

In this work, we analyzed recordings of beat-to-beat time series (RR intervals) from patients with ICDs. We classified each episode into one of two groups depending on whether the sinus rate in the minute preceding the onset of ventricular tachycardia was greater than or less than 90 beats per minute (bpm). We also analyzed changes in heart rate, several heart rate variability indexes, and several indices describing PVCs for the approximately 2 h preceding each episode of VT.

2 Materials and methods

2.1 Subjects and data

The data were collected from 1998 to 2003 from 13 patients at the Charité Hospital (12 men and 1 woman, mean age 63 ± 8 years, range 52–79 years), whose diagnosis was coronary artery disease ($n = 11$, most of them with old myocardial infarction), dilated cardiomyopathy ($n = 1$) or unknown ($n = 1$). The mean left ventricular ejection fraction was 38 ± 8. Eight patients had New York Heart Association (NYHA) class II symptoms, three had class III symptoms and two had class IV symptoms. Most patients were taking both an angiotensin converting enzyme inhibitor (ACE) or an angiotensin II receptor blocker (ARB) and beta blockers. Four of the 13 patients were on class III antiarrhythmic drugs. The study protocol was approved by the local ethics committee and the patients gave written informed consent to be enrolled, in accordance with the principles expressed by the Declaration of Helsinki. Patients received either a Biotronik Belos or microPhylax (Biotronik GmbH & Co, Berlin, Germany) ICD. These are devices with a single lead in the right ventricle. They stored 9,000 RR intervals prior to activation of a counter and therapy. In addition, the devices record the electrograms for up to 20 s preceding and following an episode of VT. Figure 1 shows an example of an electrogram from a 79-year-old woman (patient 8), which shows a transition from sinus rhythm to VT which was self

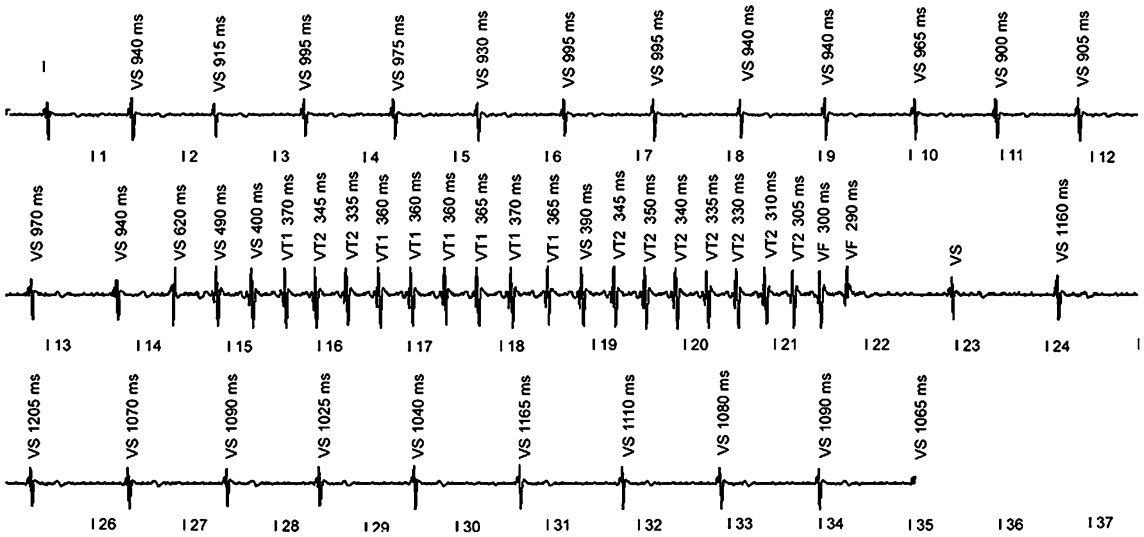

Fig. 1 Electrogram from a patient (#8) showing the transition from sinus rhythm to VT. The labels indicate ventricular sense (*VS*), ventricular tachycardia (*VT*), and ventricular fibrillation (*VF*). The VT/VF episode was self-terminated (no therapy was administered). The *marks* and *numbers* below each trace indicate the time in seconds

terminated (no therapy was administered). The preceding sinus rate was about 64 bpm without any PVCs. All episodes were classified as VT by two independent observers. The RR intervals from the VT episodes were excluded from the time series. The sampling rate was 256 Hz. These devices were programmed to deliver appropriate therapy (either antitachycardia pacing followed by a defibrillating shock or a defibrillating shock) depending on RR intervals and observed characteristics at implantation.

Each patient had (1) at least one recording preceding a VT episode, (2) at least one control recording obtained during a follow-up visit, and (3) at least one of the recordings had >10% PVCs. The total number of recordings was 68, and the total time per recording 104 ± 15 min (range 49–135 min).

The records were classified into one of two groups depending on whether the sinus rate in the minute preceding the onset of VT was greater than or less than 90 bpm. Table 1 shows the clinical characteristics and number of recordings from each group.

2.2 Heart rate variability analysis

Many methods of risk stratification for sudden cardiac death make use of data from normal sinus beats, excluding or replacing beats associated with PVCs, premature atrial contractions, or other arrhythmias. Figure 2 shows an example of RR intervals during sinus rhythm with high incidence of PVCs which looks like spikes (upper panel) or outliers (middle panel). An adaptive filtering algorithm [available on the toolbox for complex systems (TOCSY) webpage: http://tocsy.agnld.uni-potsdam.de/] was used to identify the timing intervals from premature atrial contractions and PVCs in order to replace them by interpolated values of normal RR intervals (NN) (Fig. 2, lower panel) [52]. The NN interval time series were used to calculate several heart rate variability indicators that range from simple statistical measurements in the time and frequency domains to more sophisticated measurements derived from non-linear dynamics [31, 45, 49].

Standard linear methods of HRV analysis determine time and frequency domain measures of the variation of the RR invervals [45]. The most commonly used time domain measures include the mean sinus period, "mean NN", its standard deviation, sdNN, the root mean square of successive beat-to-beat differences, RMSsd, and the percentage of beat-to-beat differences greater than 50 ms, pNN50.

Frequency domain HRV analysis investigates the power in different frequency bands [2]. In this study, the power density spectra were estimated using the Fast Fourier Transform (FFT) and applying a Blackman-Harris window function. The power in low frequency (LF) band from 0.04 to 0.15 Hz is taken as a measure of the vagal and sympathetic modulation of the heart rate via the baroreceptor reflex, whereas the high frequency (HF) band, from 0.15 to 0.4 Hz, is generally assumed to reflect the modulation of vagal activity by respiration. The ratio LF/HF was calculated, as well as the indexes LF and HF in normalized units (LFnu and HFnu, respectively). The ratio LF/HF is used as an index of sympathovagal balance [29]. The definitions and calculations of these indexes comply with the international recommendations for heart rate variability analysis [45].

Table 1 Clinical characteristics and number of recordings

	≥90 bpm (n = 6)	<90 bpm (n = 5)	Mixed (n = 2)
Age (years)	61 (52–70)	64 (54–79)	60 (57–62)
Gender (male/female)	6/0	5/0	1/1
Diagnosis			
CAD	5	4	2
DCM	1	0	0
Unknown	0	1	0
Left ventricular ejection fraction	36 (20–48)	40 (33–48)	40 (34–45)
NYHA class symptoms[a]			
II	4	2	2
III	2	1	0
IV	0	2	0
Medication			
Betablocker	5	5	2
ACE or ARB[b]	5	5	2
Diuretic	1	4	1
Digoxin	3	2	0
Antiarrhythmic drug class III	2	1	1
ICD indication			
VT	3	2	1
VF	2	0	0
VF with aborted sudden death	1	3	1
Number of recordings			
Before VT	2 (1–4)	3 (1–3)	5 (4–6)
Total before VT	12	11	10
Control	2 (1–8)	1 (1–3)	4 (2–5)
Total Control	20	8	7

According to the mean NN during the last minute before VT, there were patients with mean heart rate ≥90 beats per minute (bpm) in all recordings, or mean heart rate <90 bpm in all recordings. There were also patients with recordings in both the groups (mixed). Data are shown as median (range) or absolute values

CAD coronary artery disease, *DCM* dilated cardiomyopathy

[a] New York Heart Association

[b] Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker

Linear time and frequency domain measures do not adequately characterize the complexity of the normal sinus rhythm, and a variety of other measures often suggested by nonlinear dynamical approaches have been used to characterize HRV. One method uses symbolic representations of the heart rate [53]. Because of the close association of these measures with definitions of entropy in physical science, such measures reflect in a natural way the complexity of the fluctuations of the heart rate [21, 49, 53]. The symbolic parameters, both FWShannon and Forbidden Words are based on an alphabet consisting of four symbols [49]. FWShannon denotes the Shannon-entropy of the word distribution whereas Forbidden Words stands for the number of words, which never or very seldom occur. Larger values of FWShannon reflect higher complexity, whereas a high number of Forbidden Words reflect a rather regular behavior.

Another measure that has been used to characterize HRV is generated by considering a symbolic series which consists of two symbols "0" and "1", where "0" represents a difference between two successive sinus intervals of less than 10 ms, whereas "1" represent a difference between two successive sinus intervals of greater than 10 ms. The statistic "polvar10" is the relative frequency of the word "000000" out of all the 64 different words of length 6. Polvar10 is elevated during episodes of decreased heart rate variability, and is elevated even if there is intermittently decreased variability [50].

2.3 Analysis of ventricular arrhythmias

Since arrhythmic cardiac death is often associated with an increased incidence of PVCs [7, 40, 44], several methods of risk stratification focus on the analysis of PVCs. Such methods include counting the number of PVCs [1, 7], heart rate turbulence (which measures the short-term effect of isolated PVCs upon the heart rate) [15, 41] and fractal measures that are sensitive to the time clustering of PVCs [4]. However, those methods cannot provide more subtle information about the mechanisms of arrhythmia. We have hypothesized that the dynamics of PVCs over long times provide information about the arrhythmic mechanisms. Furthermore, some mechanisms may be manifested in specific complex forms of ventricular arrhythmia that may

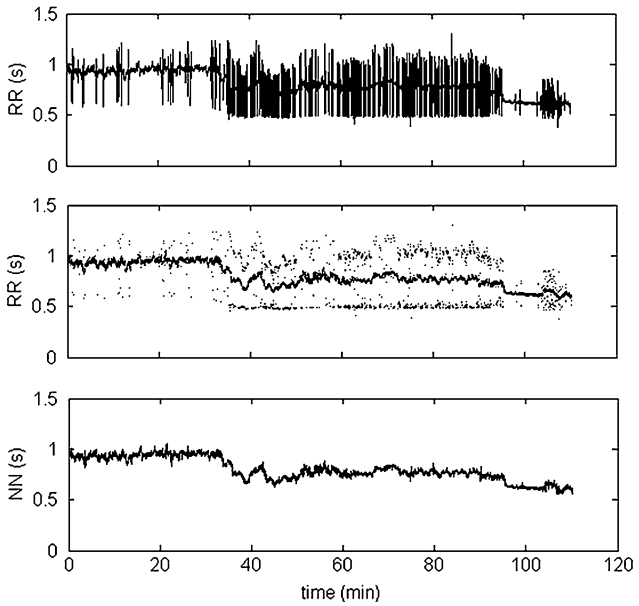

Fig. 2 Example of RR interval time series during sinus rhythm with high incidence of premature ventricular complexes (PVCs) that look like "spikes" (*upper panel*) or as "outliers" (*middle panel*) and that were detected and replaced by an adaptive algorithm (*lower panel*)

be linked to identifiable and predictable changes in heart rate leading to VT or VF [26, 42].

Based on the stored RR intervals that were processed by the adaptive filtering algorithm [52], each beat was labeled as a normal beat (N), or a PVC (V). Then each pair of successive RR intervals was identified as NN, NV, VN or VV. Color-coded RR interval time series, heartprints [26, 42] and persistence plots [26], described below, were generated using custom written Matlab software (The MathWorks, Inc., Natick, MA). The ventricular arrhythmias are classified based on the composition of their repeating sequences: bigeminy (VNV), trigeminy (VNNV), quadrigeminy (VNNNV). We designate the number of intervening sinus beats (N) between two consecutive V beats as the NIB value. Therefore, bigeminy, trigeminy and quadrigeminy are sequences of NIB values equal to 1, 2 and 3, respectively. Concealed bigeminy is defined as repetitive sequences of NIB values that are all odd numbers. Sequences of consecutive V beats (NIB value = 0) were classified as couplets (two consecutive V beats) or as non-sustained VT (3 or more consecutive V beats that spontaneously terminate). The coupling interval (CI) is the time duration from an N beat to the immediately following V beat. As described previously [26, 42] we use these data to generate novel visualizations that reflect the dynamics of ventricular arrhythmias. An arrhythmia was considered persistent if 5% or more PVCs of the entire recording were involved in repeating sequences of at least five cycles of the corresponding sequence.

2.4 Statistical analysis

Ordinal variables are expressed as median (range), and were tested for normality of distribution by a Kolmogorov–Smirnov test before applying *t* tests or by Wilcoxon rank sum tests according to the normality test results. Nominal variables are shown as absolute values and were compared by Chi-squared tests. A *P* level of <0.05 was considered as a cut-off for statistical significance.

3 Results

3.1 Heart rate variability analysis

Figure 3a shows a scatter plot of the mean NN interval in the 1 min prior to VT compared to the mean NN during the entire record preceding that episode of VT. Based on these data we have divided the instances of VT onset into two groups depending on whether the mean heart rate in the 1 min preceding VT is greater or less than 90 bpm. Except for patients 11 and 16, all the episodes of VT in a given patient occurred either during the higher or the lower range of sinus rate. Figure 3b summarizes the evolution of the mean NN interval in the 5 min preceding VT for each episode of VT and for each control tracing. With the exception of four instances, the mean NN interval was in either the upper or the lower group for the entire 5 min prior to VT.

In order to characterize the HRV further, in Table 2 we show the comparisons of all the HRV indexes calculated over the duration of the records. No time domain parameter detected significant differences either between the VT and control series groups or between the heart rate greater or less than 90 bpm groups. In the frequency domain, LF and HF were significantly decreased before VT in the group with heart rate >90 bpm compared with the group with heart rate <90 bpm. Probably, a higher sympathetic tone in the group with heart rate >90 bpm leads to a decreased HRV and thus to decreased LF and HF. This increased sympathetic tone is also detected by the symbolic dynamics parameter Polvar10.

To further explore changes in HRV characteristics prior to VT, we compare the mean NN and Polvar10 over 5 min intervals for the 30 min prior to VT (Fig. 4). Prior to the onset of VT, the mean NN was significantly different between both the groups (>90 bpm vs. <90 bpm), as early as 15 min before VT (indicated by the asterisks). In the group with heart rate >90 bpm before VT, the mean heart rate increased significantly with respect to the control recordings as early as 25 min before VT (indicated by the symbols ¶).

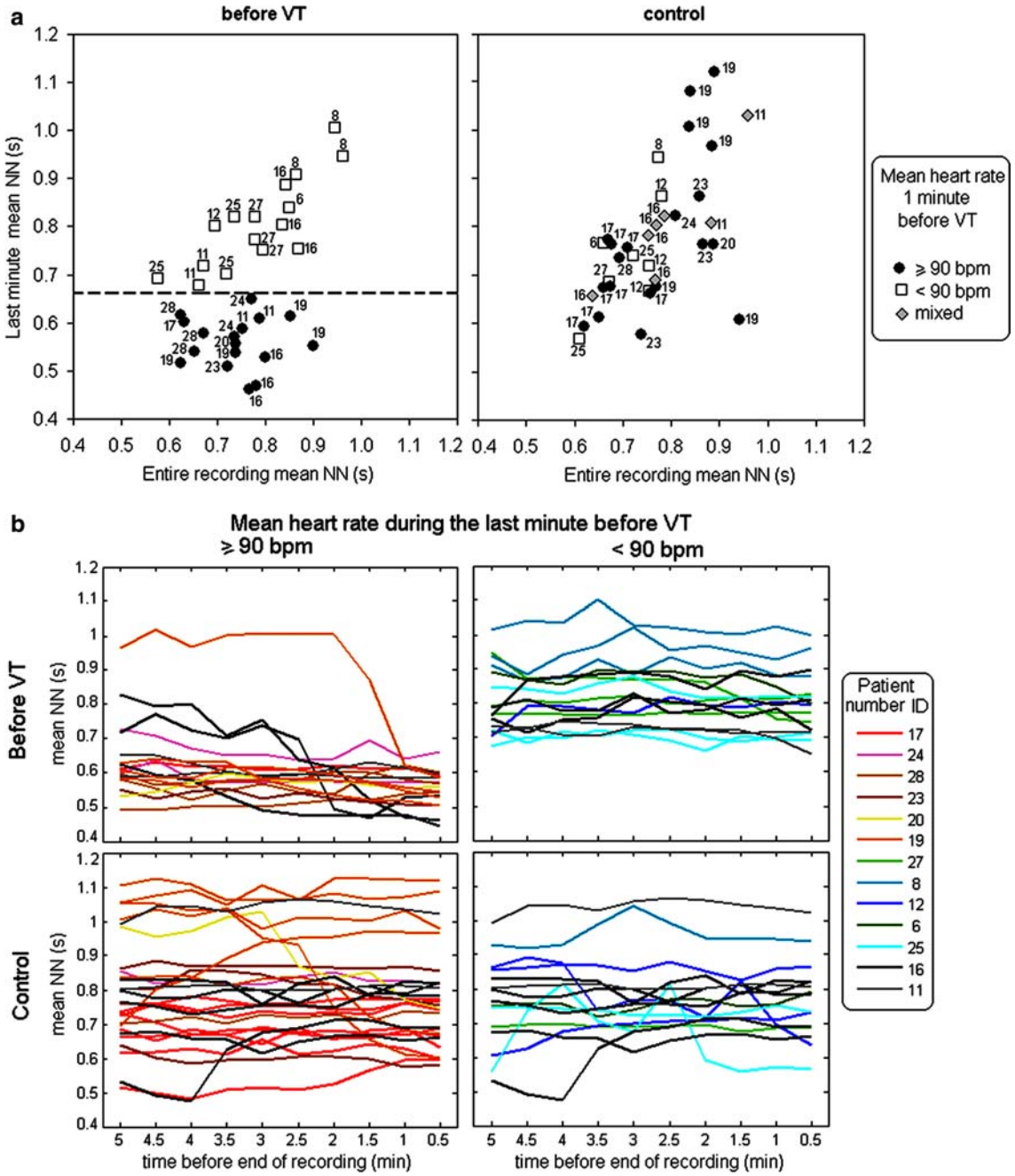

Fig. 3 (Color online) Mean NN from all recordings. **a** Last minute mean NN versus overall mean NN. The points below the *horizontal dotted line* indicate the recordings were mean NN ≤667 ms (mean heart rate ≥90 beats per minute) during the last minute prior VT. The *number close to each point* indicates the patient ID number. **b** Last 5 min mean NN before the end of recording, averaged each 30 s. The recordings were grouped the same way as in **a**. Each *color* corresponds to a different patient

Prior to the onset of VT, Polvar10 was significantly different between both the groups (>90 bpm vs. <90 bpm), as early as 20 min before VT (indicated by the asterisks). In the group with mean NN>90 bpm before VT, Polvar10 was significantly higher before VT than in control recordings, as early as 25 minutes before VT (symbols ¶).

3.2 Ventricular arrhythmias analysis

The techniques we used to analyze the ventricular arrhythmias characteristics allowed us to identify different patterns of arrhythmia. Two detailed examples follow and are summarized in Figs. 5 and 6.

Table 2 Heart rate variability analysis of the *entire recording period*, percentage of PVCs and characteristics of the VT episodes

Index	Mean heart rate ≥90 bpm		Mean heart rate <90 bpm	
	Before VT ($n = 17$)	Control ($n = 27$)	Before VT ($n = 16$)	Control ($n = 15$)
Mean NN (s)	0.74 (0.62–0.9)	0.77 (0.62–0.96)	0.79 (0.58–0.96)	0.76 (0.61–0.96)
sdNN (ms)	29 (21–67)	34 (15–70)	41 (14–65)	46 (14–60)
RMSSD	14 (7–41)	15 (7–62)	22 (9–61)	16 (7–32)
pNN50 (%)	0.01 (0–0.17)	0.01 (0–0.26)	0.03 (0–0.27)	0.01 (0–0.10)
LF (s^2)	0.01 (0–0.05)*	0.02 (0–0.08)	0.03 (0–0.09)	0.03 (0–0.08)
HF (s^2)	0.004 (0–0.03)*	0.01 (0–0.07)	0.01 (0–0.04)	0.01 (0–0.02)
LFnu	0.69 (0.46–0.85)	0.77 (0.50–0.83)	0.67 (0.55–0.89)	0.79 (0.55–0.88)
HFnu	0.31 (0.15–0.54)	0.23 (0.17–0.5)	0.33 (0.11–0.45)	0.21 (0.12–0.45)
LF/HF	3 (0.9–8.5)	4 (1.2–5.3)	2.3 (1.4–9.4)	4.2 (1.5–9)
Shannon	1.66 (1.16–2.37)	1.82 (1.12–2.47)	1.91 (1.11–2.29)	2 (1.05–2.28)
FWShannon	2.1 (1.6–3.1)	2.1 (1.5–3.2)	2.6 (1.9–3.4)	2.3 (1.6–2.8)
Forbidden Words	39 (16–50)	41 (14–54)	35 (16–50)	39 (23–50)
Polvar10	0.28 (0.04–0.58)*	0.15 (0–0.57)	0.07 (0–0.4)	0.07 (0–0.62)
PVCs (%)	2 (0–50)	1 (0–22)	7 (0–32)	2 (0–14)
RR_{n-1} (ms)	430 (335–620)		415 (335–980)	
VTCI (ms)	325 (225–445)		348 (300–435)	
CI/RR_{n-1}	0.75 (0.52–1.02)		0.83 (0.44–0.96)	
VT cycle length (ms)	283 (196–447)		308 (269–413)	

Recordings were grouped according to the mean heart rate during the last minute before VT. The data are shown as median (range), nu means normalized units. All HRV indexes except mean NN were calculated from the filtered RR intervals time series

RR_{n-1} RR interval prior to the onset of VT, *VTCI* VT coupling interval

* Significant difference ($P < 0.05$) between recordings with heart rate ≥90 bpm before VT and recordings with heart rate <90 bpm before VT

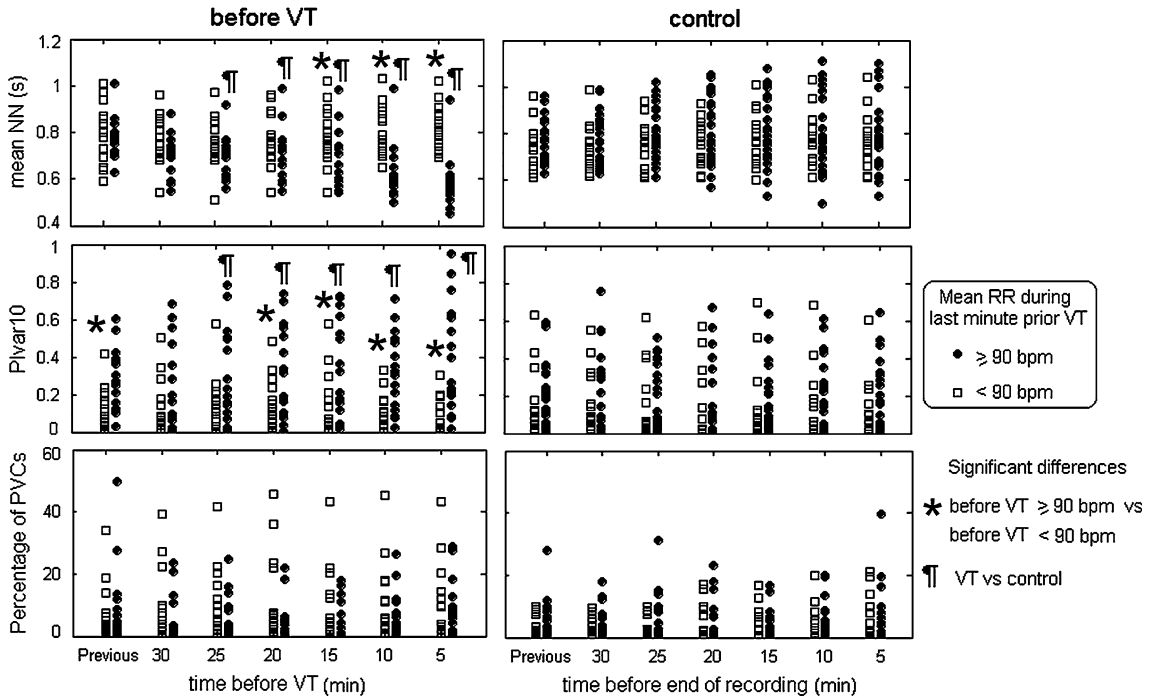

Fig. 4 Mean NN, Polvar10 (probability of low variability) and percentage of PVCs before the end of recordings. The *dots* or *squares* correspond to the average of 5 min from each and every recording. The recordings were grouped according to the mean NN during the last minute before VT: mean NN ≥ 90 beats per minute (bpm) or <90 bpm. The mean NN was calculated from only NN intervals (the RR intervals involving ectopic beats were excluded instead of being interpolated)

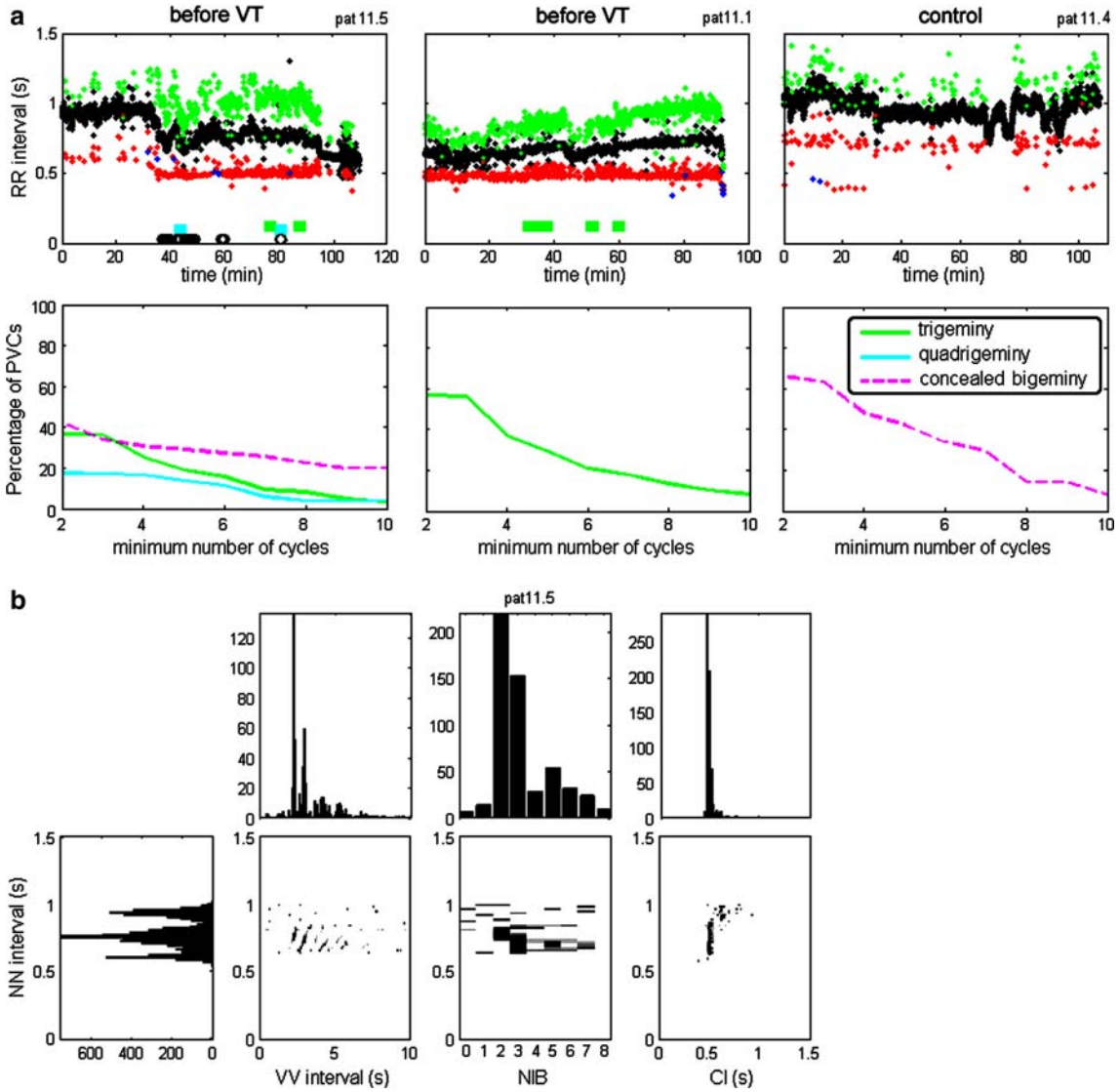

Fig. 5 (Color online) Ventricular arrhythmias analyzed in a 57 year old female (patient #11) with coronary artery disease post myocardial infarction and documented VT and VF with mean heart rate ≥90 beats per minute during the last minute before VT. **a** Time series (*first row*) shows that before VT, the patient had acceleration or heart rate (episode 5, *left*) or very fast baseline heart rate (episode 1, *middle*) and high incidence of PVCs in the form of trigeminy, quadrigeminy and concealed bigeminy. The heart was slower during the control recording (episode 4, *right*). There was higher incidence of PVCs before VT (higher density of *colored dots*). Persistent episodes of trigeminy and quadrigeminy were observed only before VT, but not during the control recording. The occurrence of the arrhythmias persistent for at least ten cycles is indicated at the *bottom* of the time series plots by *green* and *blue boxes*, and *black circles* for trigeminy, quadrigeminy and concealed bigeminy, respectively. **b** Heartprint from one recording before VT showing high incidence of NIB numbers 2 and 3, with NN intervals between 0.5 and 0.8 s and a fixed CI

Figure 5a shows the color-coded RR interval time series (upper row) of a 57-year-old woman with coronary artery disease post myocardial infarction (patient #11). The NN intervals are designated by black dots, NV intervals by red dots, VN intervals by green dots, and VV intervals by blue dots. Before VT, there was increased heart rate (left) or a very fast baseline heart rate (middle), while during control the heart rate was slower (right). There were frequent PVCs before VT with a relatively fixed CI = 0.5 s. The persistence plots [26] in Fig. 5a (lower row) show the percentage of PVCs involved in each ventricular rhythm as a function of the minimum number of repeating sequences required to identify a succession of RR intervals as belonging to that rhythm. For example, in Fig. 5, first lower panel, the green line indicates that about 5% of the PVCs were involved in ventricular trigeminy of at least 10 repeating sequences of the basic sequence VNNV (or NIB = 2), while the dashed pink lines indicate that 20% of the PVCs were involved in concealed bigeminy (with NIB values that are only odd numbers).

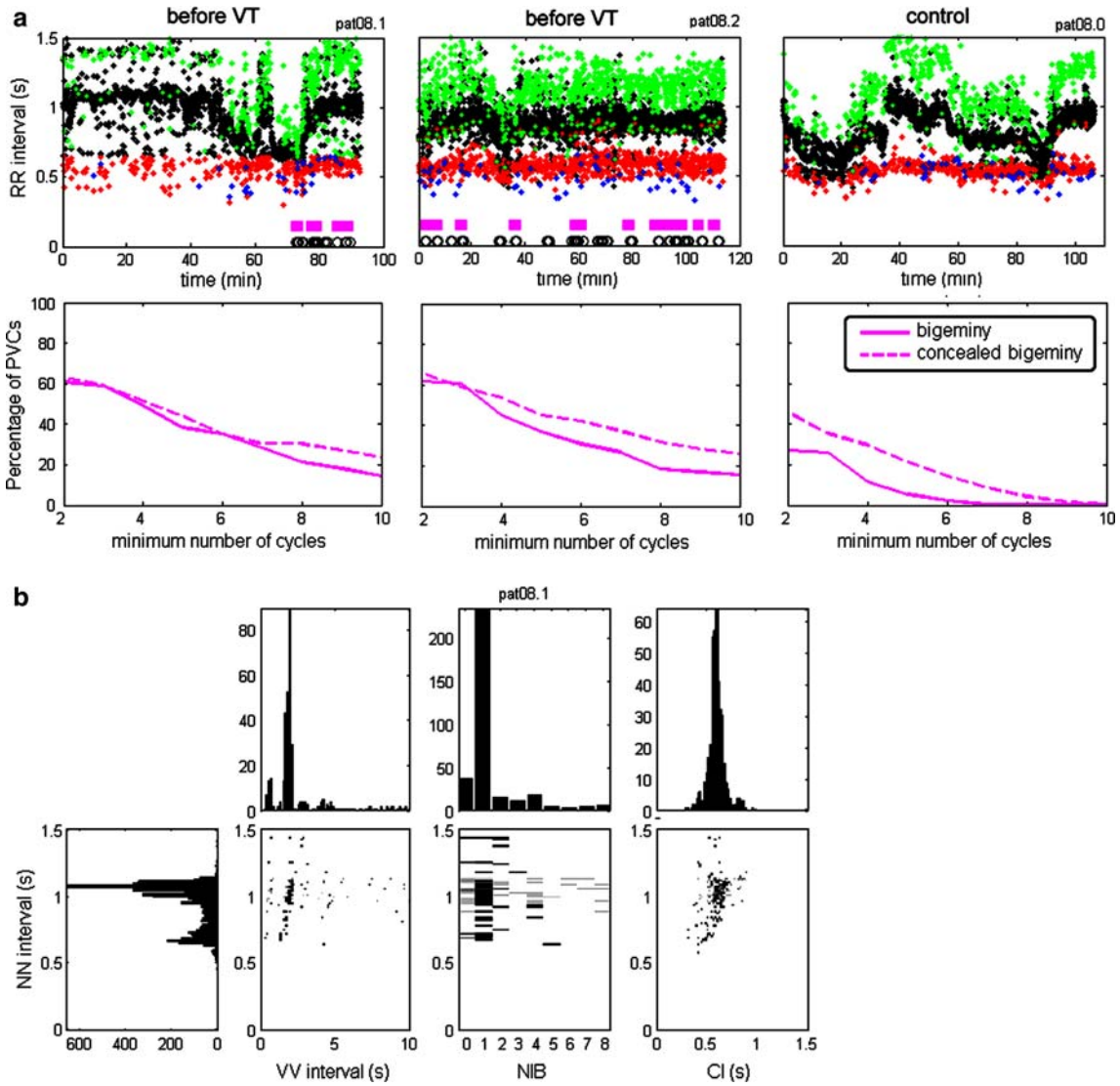

Fig. 6 (Color online) Ventricular arrhythmias analyzed from a 79 year old female (patient # 8) with documented VF and sudden cardiac death from unknown etiology with mean heart rate <90 beats per minute during the last minute before VT (sample of electrogram in Fig. 1). **a** Time series (*first row*) shows that before VT, the patient had decelerated heart rate (episode 1, *left*) or no change in heart rate (episode 2, *middle*) and high incidence of PVCs in the form of bigeminy and concealed bigeminy. The heart rate fluctuated and had a high incidence of PVCs during the control recording (episode 0, *right*). Persistence plots show that episodes of bigeminy were more persistent before VT than during the control recording. The occurrence of the arrhythmias persistent for at least ten cycles is indicated at the *bottom* of the time series plots by *pink boxes* for bigeminy and by *black circles* for concealed bigeminy. **b** The heartprint showed very persistent bigeminy and concealed bigeminy (NIB = 1) mostly at slow heart rates (NN intervals between 0.75 and 1.25 s), and with variable CI

In order to represent the sinus rate-dependent changes in the patterns of PVCs, we have developed the heartprint ([26, 42], Fig. 5b). The ordinate of the three grayscale plots in the heartprint is the NN interval. The incidence of the VV intervals, NIB values, and the CI are indicated in the three grayscale plots, respectively, where darker shades indicate increased incidence. The plots above the grayscale plots give the histograms of the VV intervals, the NIB values, and the CI, respectively. The histogram to the left of the grayscale plots gives the histogram of NN values. Figure 5b shows that prior to the onset of VT, trigeminy (NIB = 2) was prevalent for longer NN intervals, quadrigeminy (NIB = 3) was prevalent for shorter NN intervals, and the CI was relatively fixed for all heart rates. In contrast, analysis of the control rhythm displays episodes of concealed bigeminy (Fig. 5a, right lower row). The tachycardia initiated in episode 5 (Fig. 5, left upper panel) was terminated by antitachycardia pacing, consistent with a reentrant mechanism for the VT in this episode. The differences in CIs and patterns of arrhythmia in the records

that precede tachycardia and those occurring during control, suggest the possibility of different mechanisms of arrhythmia in this patient.

A different pattern was observed in a 79-year-old female patient (#8) with documented sudden cardiac death and VT from unknown etiology (a sample electrogram from this patient is shown in Fig. 1). Figure 6a (upper row) shows a slower heart rate preceding VT. The persistence plots (Fig. 6a, lower row) and the heartprint (Fig. 6b) show that there was a high incidence of PVCs occurring in predominantly bigeminal or concealed bigeminal rhythms with a comparatively broad range of CIs in the range 0.5–0.6 s. During the control recording there was a reduced incidence of PVCs, but the characteristics were similar to those preceding VT. In this patient, VT was only observed at slower heart rates. This patient exhibited nonsustained VT that was not immediately preceded by PVCs, Fig. 1. The mechanism of the VT here is unknown.

The incidence of ventricular arrhythmia was highly heterogeneous; some patients had a high incidence of PVCs in some recordings and a low incidence of PVCs in other recordings. Although there was a trend of higher frequency of PVCs prior to VT compared to control recordings (Fig. 4), the difference was not statistically significant (Table 2). Yet, there were several episodes of VT which were not preceded by a significant incidence of PVCs. Furthermore, although persistent arrhythmias were often observed in recordings before VT (24 out of 33 recordings before VT and 24 out of 42 control recordings), since they were not common during the last 5 min prior to the end of recording persistent arrhythmia (they occurred only in 7 out of 33 recordings before VT and 2 out of 42 control recordings), they do not appear to have a clear significance in the current set of patients.

4 Discussion

The transition from normal sinus rhythm to VT has been the subject of intensive investigation for many years [5, 9–11, 16, 19, 20, 24, 26–28, 30, 31, 34, 37, 46, 47]. This literature makes it clear that the events preceding the onset of VT might be quite different in different patients with similar clinical histories. For example, in early studies Leclercq et al. [24] documented an important role for sympathetic activity as evidenced by an accelerated heart rate in a subset of coronary patients experiencing sudden death during Holter monitoring. In these patients, although some instances of VT are associated with immediately preceding PVCs, it is also common to find a spontaneous initiation of VT/VF without immediately preceding short-long cycles induced by PVCs. Subsequent studies have further documented the heterogeneity of events preceding VT [11, 30, 37], and also the role of accelerated sinus rates in a subgroup of patients prior to VT onset [31].

Our research confirms and extends these earlier observations. Due to the availability of long recordings of RR intervals, we were able to analyze the HRV indices for 30 min preceding the onset of VT. One measure, Polvar10, which measures the incidence of 6 beat segments during which the beat-to-beat difference of RR intervals is less than 10 ms, gave significant changes with respect to control as early as 20 min prior to the VT onset, Fig. 4. This change reflects the presence of laminar phases in which there are small changes of the RR interval [31, 50, 53]. Although the significance of Polvar10 needs to be investigated more closely in larger populations, and under different sampling frequencies, the current work suggests the possibility of finding a new easily measurable premonitory factor up to 20 min prior to VT onset in selected patients.

Previous studies on patients with ICDs, examined the role of PVCs but did not analyze the patterns of arrhythmias in detail [9, 10, 25, 37]. In our earlier studies, we found characteristic patterns that reflect the physiological mechanisms for patients with parasystole (variable CIs, and striking predicted changes of NIB sequences as a function of sinus rhythm) [42] and in patients with a long QT interval and polymorphic VT (predominant bigeminal rhythms with fixed CIs over a range of sinus rates) [26]. In this latter class of patients, the onset of polymorphic VT occurred at slow heart rates consistent with a hypothesized mechanism of early afterdepolarizations. None of the records analyzed in the current study displayed either of these two phenotypes. Although in the current study one patient displayed predominantly bigeminal rhythms and the VT onset occurred at slower heart rates, the CIs in this patient were variable and VT was not in general initiated after a long pause, Figs. 1 and 6.

Since most of these patients had a prior myocardial infarct, it is likely that the mechanism for VT in several of them was associated with a reentrant pathway. Although it has been previously shown that a reentrant mechanism could lead to bigeminal and trigeminal rhythms [42], theoretical analysis of the observed patterns of ectopy in Fig. 5 remains a challenge for future work.

One of the patients (#19) had a successful ablation of a right ventricular outflow tract tachycardia subsequent to the recordings in this study. This observation is consistent with the findings that the VT in this patient occurred at sinus rates >90 bpm (Fig. 3), and it agrees with earlier observations of enhanced sympathetic tone in the initiation of VT originating from the right ventricular outflow tract [12].

Although our expectation was that we would find distinctive patterns of heart rate variability and ectopy in individual patients and in patients with similar clinical conditions, the data indicate great variability in some

individuals at different times and also between individuals. These reflect differences in physiological mechanisms between individuals and well as differences in physiological state due to uncontrolled variables such activity, drugs, and disease progression. Although from a clinical perspective, it is essential to carry out clinical studies that assess risk factors over large populations to guide physicians' therapeutic decisions, the great variability among patients indicates that it is important to continue to analyze the mechanisms of arrhythmias with a view of developing quantitative models that are capable of being compared with data from individual patients. The current work makes clear that such models will necessarily have to consider the role of sympathetic tone and its interaction with mechanisms generating tachyarrhythmias.

4.1 Limitations

The current analysis was carried out retrospectively on a small sample of patients ($n = 13$) with an ICD. In order to examine the characteristic of HRV and PVCs, we only selected patients who had at least 10% of the beats as PVCs. This has biased the records in two ways. First, it omits patients who do not have PVCs. Further, the presence of PVCs can in some cases lead to inaccurate assessment of HRV, since many algorithms replace or remove ectopic beats and use interpolation to determine a corrected sinus rate. The ICDs only had one lead. This makes definitive identification of VT difficult. For example, in some patients there is close similarity of the ventricular electrogram during the tachycardia and the preceding sinus beats. Although the rapid rate and the clinical situation make it likely that the arrhythmia in these cases is due to VT, there is nevertheless a possibility that the arrhythmia is a supraventricular tachycardia with rapid conduction. The automatic identification of PVCs based on the timing of intervals represents another source of error. In cases where there is a very irregular rhythm, as in atrial fibrillation, the algorithm does not work and such patients could not be considered. In some cases, the automatic identification leads to errors. In cases in which these are obvious, the record was not considered. Furthermore, our methods do not distinguish between complexes arising from supraventricular or ventricular activity and all premature complexes are attributed to ventricular activity. Many of these problems would be mitigated using an ICD that has both atrial and ventricular leads and further studies with such data would be useful.

5 Conclusions

There is widespread agreement that there is a need for better risk stratification for sudden cardiac death [3, 11, 14]. The current study develops a multifactorial analysis of a unique data set in a limited number of patients. We identified a subset of patients ($n = 6$) who experienced accelerated heart rate and a significantly decreased value of Polvar10 as early as 20 min before the onset of VT. In a second group ($n = 5$), there was relatively constant or decelerated heart rate during the last 5 min prior to VT. The heartprints, which reflect the patterns of ventricular ectopic beats in these patients showed evidence of persistent rhythms such as bigeminy, concealed bigeminy, and trigeminy, but there did not appear to be distinctive arrhythmic patterns that could be used to predict the imminent onset of VT. The current work further underscores the difficulty of risk stratification for sudden cardiac death. However, it also makes clear that the physiological mechanisms underlying the transition from sinus rhythm to VT is different in different patients. We believe that detailed analysis and classification of multiple physiological markers, including heart rate, patterns of ectopy, clinical history, and so forth will be essential to analyze and understand the mechanisms underlying the transition to VT and the risk for sudden cardiac death in individual patients. Thus, detailed analysis of cardiac activity and correlations between arrhythmia and sinus rate over extended times may provide methods for improving risk stratification for sudden cardiac death.

Acknowledgments The authors thank the CIHR and MITACS for financial support. J. K. and N. W. acknowledge financial support by the EU Network of Excellence, Grant No. NoE 005137 BioSim, as well as by the Deutsche Forschungsgemeinschaft Grants Nos. KU 837/23-1 and KU 837/20-2.

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