RR interval analysis based on a newly developed PC program as a predictor of interventions in implantable cardioverter-defibrillator patients

Michał Lewandowski[A–F], Ilona Kowalik[C,E,F]

National Institute of Cardiology, Warszawa, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Address for correspondence
Michał Lewandowski
E-mail: mlewandowski@ikard.pl

Abstract

Background. Prediction of sudden cardiac death remains a significant challenge. There is some evidence that ventricular ectopic activity could be regarded as a predictive marker.

Objectives. We carried out an analysis to explore whether premature ventricular complexes (PVCs) are a risk factor in implantable cardioverter-defibrillator (ICD) interventions.

Materials and methods. The study method was a RR interval series analysis (n = 184) of arrhythmic events and controls from the ICD. Study group consisted of patients with a mean age of 55 ±27 years; 74% of them were male, 85% were secondary prevention patients, 62% had coronary artery disease (CAD), 15% hypertropic cardiomyopathy (HCM), 15% dilated cardiomyopathy (DCM), and 8% diseases of other etiology. The mean follow-up time was 64 months (range: 3–126 months). The study population was divide into patients with at least 1 appropriate intervention ventricular tachycardia/ventricular fibrillation (VT/VF) (group A, n = 101) and controls without interventions (group B, n = 83). The number of PVC/4000 RR cycles, the shortest coupling intervals between a PVC and preceding R as well as the number of PVCs of very short (180–220 ms), short (220–280 ms) and different cycle lengths (CL) as well as the incidence of short-long-short (SLS) sequences were compared.

Results. The number of PVCs/4000 RR cycles was significantly higher in group A (263 ±32 compared to 43 ±17, p < 0.0001). The mean shortest PVC CL was significantly shorter in group A (320 ±13 compared to 400 ±38, p = 0.029). The number of PVCs with a very short CL was 1 ±0.4 compared to 0.1 ±0.1 (p = 0.028). The number of PVCs with a short CL was 5 ±1.2 compared to 0.6 ±0.4 (p = 0.0007) in groups A and B, respectively. The incidence of SLS sequences was significantly higher in group A than in group B (67 (94% of patients) and 4 (33% of patients) respectively (p < 0.0001)).

Conclusions. Significant differences were found in the characteristics of PVCs and SLS sequences between patients with appropriate ICD interventions and controls. A newly developed basic computer program called PCRR was applied for RR interval analysis. This simple method could be a predictor of PVC burden and life-threatening arrhythmias in different populations.

Key words: implantable cardioverter-defibrillator, initiation of ventricular fibrillation and ventricular tachycardia, sudden cardiac death prevention, premature ventricular complexes, RR interval

Background

The implantable cardioverter-defibrillator (ICD) has been a primary therapy for the treatment of life-threatening arrhythmias for 4 decades. While having a powerful therapy for sudden cardiac death (SCD) prevention is a boon to medicine, the mechanisms leading to fatal outcomes are still not fully understood. Extensive studies concerning mechanisms of initiation of ventricular tachyarrhythmias started in the last 2 decades of the 20th century. Since the publication by de Luna, Coumel and Leclercq in 1989, this clinical problem has been better understood.[1] Recently, more studies have revealed some insight into the mechanisms of SCD.[2–4] Heart rate variability (HRV), QT dispersion, baroreflex sensitivity (BRS), and T wave alternans have been described as predictors of cardiovascular mortality. Nevertheless, prediction of SCD is still a challenge. Nowadays, ICD technology allows us to store information about the actual heart rhythm and the onset of arrhythmias, so that the electrical trigger of the event can be investigated. An experienced cardiologist can easily distinguish between various kinds of RR patterns and discriminate whether a particular episode is a benign or a lethal one by assessing the series of RR intervals presented in the form of intracardiac electrograms (IEGM). Knowledge of typical kinds of tachycardias and common electrocardiography (ECG) understanding is used to recognize arrhythmias. In the present study, we attempted a scientific assessment of various types of patterns in order to identify the one which carries the biggest "risk" on the basis of RR values, rather than relying on a subjective assessment by a physician.

Most of re-entrant arrhythmias occur due to unidirectional block and premature beats. There is some evidence that abrupt changes in cycle lengths may facilitate tachycardia initiation.[5] The Purkinje system and premature ventricular complexes (PVCs) have been shown to play an important role in the initiation of ventricular tachycardia/ventricular fibrillation (VT/VF).[6–9] The short-long-short (SLS) sequence increases the dispersion of repolarization and may also facilitate re-entry.[3] The PVC and SLS sequence examples are presented in Fig. 1A. In this IEGM, a SLS sequence (RR intervals 590 ms, 992 ms and 422 ms) initiates VT/VF. Antitachycardia pacing (ATP) was unsuccessful in terminating the arrhythmia; high-voltage therapy of 36 J which terminates the arrhythmia was required ("return to sinus", Fig. 1B).

Objectives

The aim of this study was to analyze whether PVCs remain a risk factor for appropriate ICD interventions and to categorize cardiac rhythm episodes of device
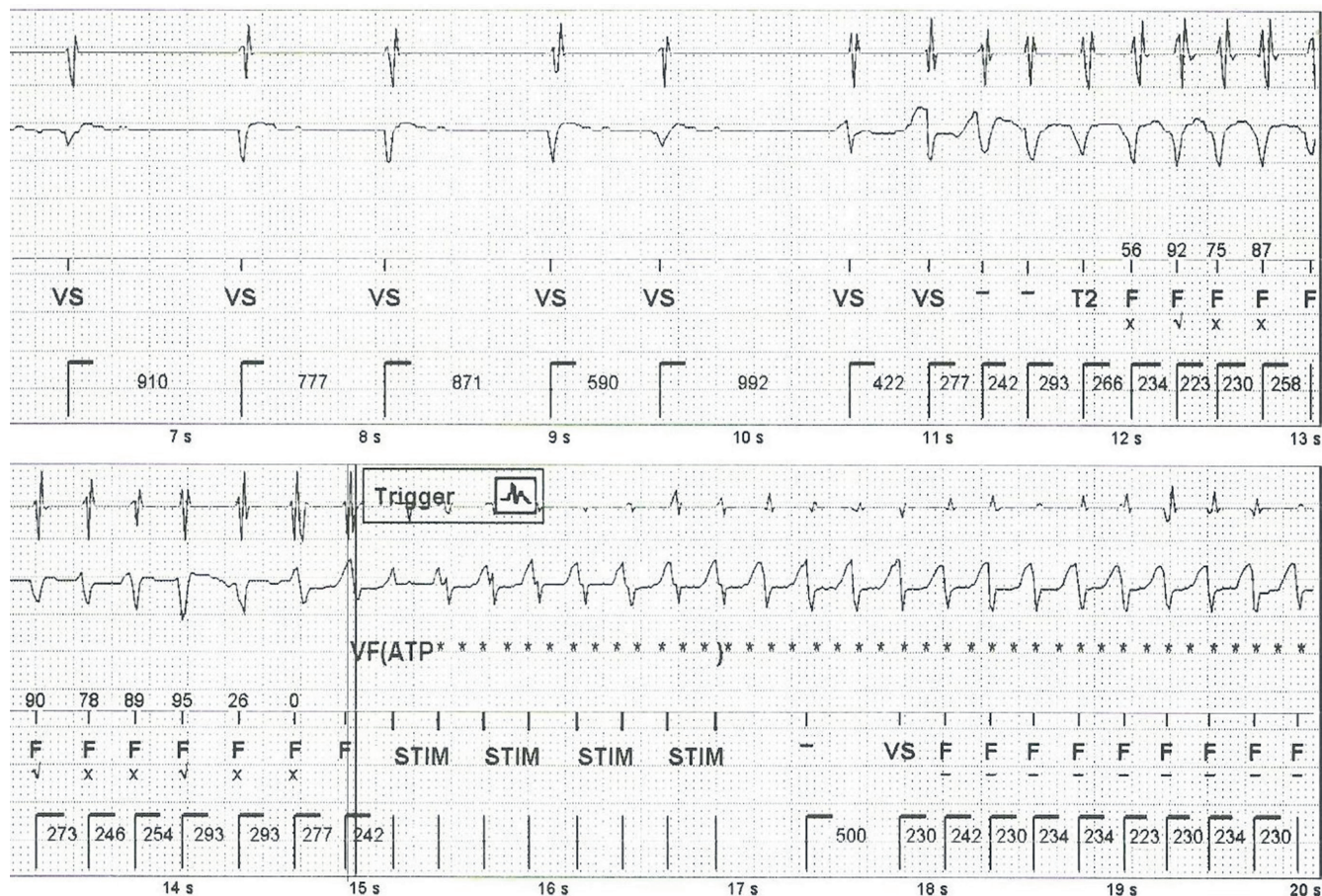

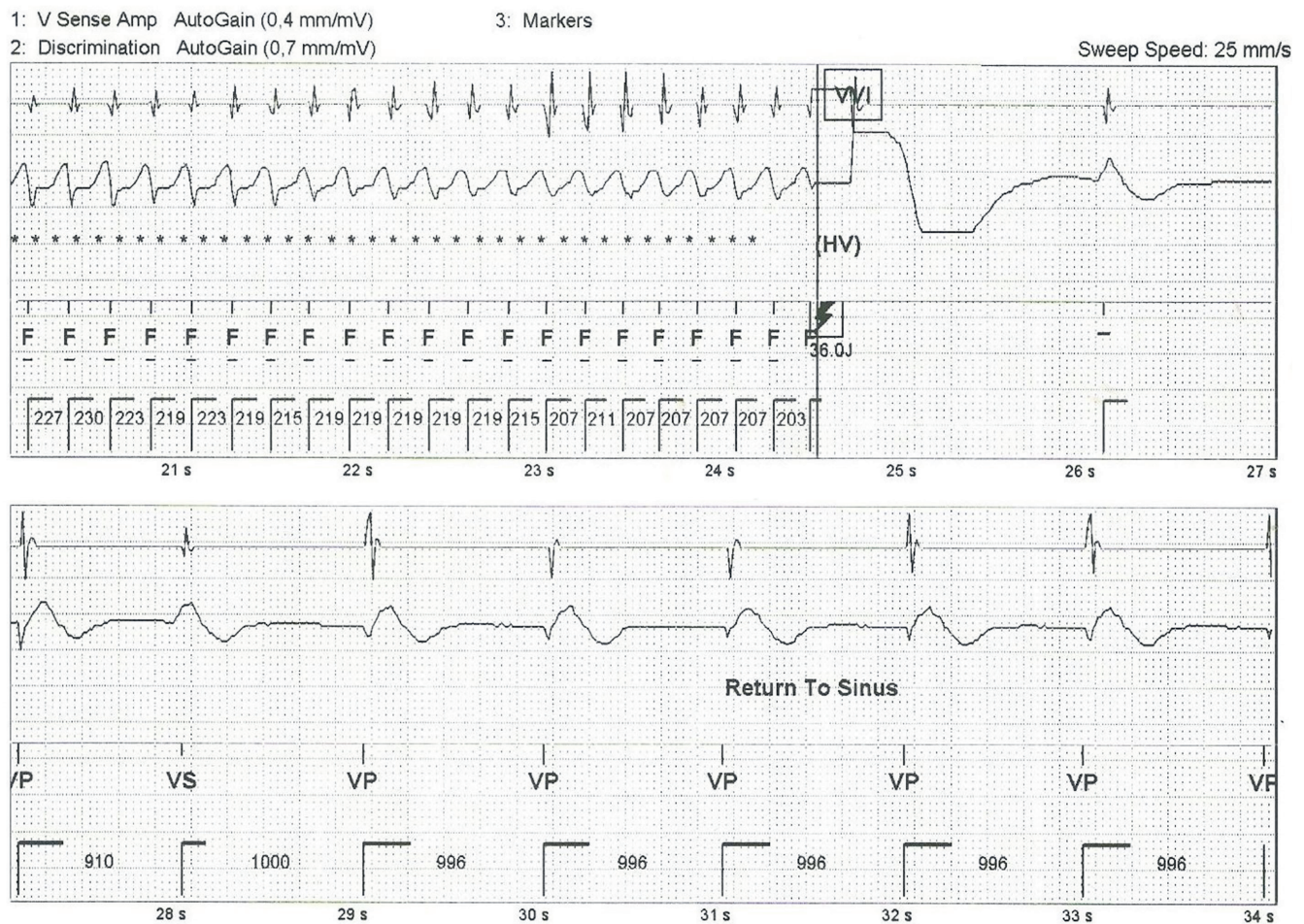Fig. 1A. The IEGM of the PVC and short-long-short sequence

1: V Sense Amp   AutoGain (0,4 mm/mV)   3: Markers

2: Discrimination   AutoGain (0,7 mm/mV)

Sweep Speed: 25 mm/s

VVI

(HV)

36.0J

F F F F F F F F F F F F F F F F F F F F

227 230 223 219 223 219 215 219 219 219 219 219 215 207 211 207 207 207 207 203

21 s   22 s   23 s   24 s   25 s   26 s   27 s

Return To Sinus

/P   VS   VP   VP   VP   VP   VP   VP

910   1000   996   996   996   996   996

28 s   29 s   30 s   31 s   32 s   33 s   34 s

Fig. 1B. The short-long-short sequence cycle impact on ICD intervention

interrogation. If possible with the proposed methodology, it could be used as a relative simple predictor of PVC burden and life-threatening arrhythmias in patients without an ICD. The paper thus presents a new computer program for cardiac RR interval analysis and its potential application for the internet data transfer.

Materials and methods

Study group

Consecutive patients were divided into those with at least 1 appropriate intervention due to VT/VF in the form of ATP or high-energy therapy (group A, n = 101) and controls without ICD intervention revealed during device interrogations in the follow-up (group B, n = 83). Group B included RR intervals extracted during a scheduled clinical visit from device interrogations of ICDs in 2 subgroups of patients: 1) 31 patients in whom the interrogation was not preceded by any therapy, i.e., who did not experience any cardiac arrhythmias; and 2) 52 patients from group A in whom interrogations did not precede ICD therapy (comparison

of the episodes was done within the same patients, i.e., episodes not only before the therapy but also remote from the therapy were included). Thus, the study group consisted of 131 patients, while 184 RR interval series were analyzed. The mean follow-up was 38 months (range: 12–64 months).

The number of PVC/4000 RR cycles, the shortest coupling intervals (CI) between PVCs and preceding R, the number of PVCs of very short cycle lengths (180–220 ms) and short CI (220–280 ms), PVC of different CI, the incidence of non-sustained ventricular tachycardia (NSVT), and the incidence of SLS sequence (defined as RR 2 < 75% of the last 4 RR intervals of the underlying rhythm, followed by RR 3 > 75% of the last 4 cycles) were examined and compared. An example of NSVT is presented in Fig. 2.

For PVC analysis, 2 models were defined: coupling interval between PVC and preceding R defined as RR interval >10% than the predecessor of the underlying rhythm (model 1) and RR > 20% than the predecessor of the underlying rhythm (model 2).

For the analysis of the RR intervals, searches for the rate and values of the phenomena defined in the protocol, a computer program was developed by an experienced
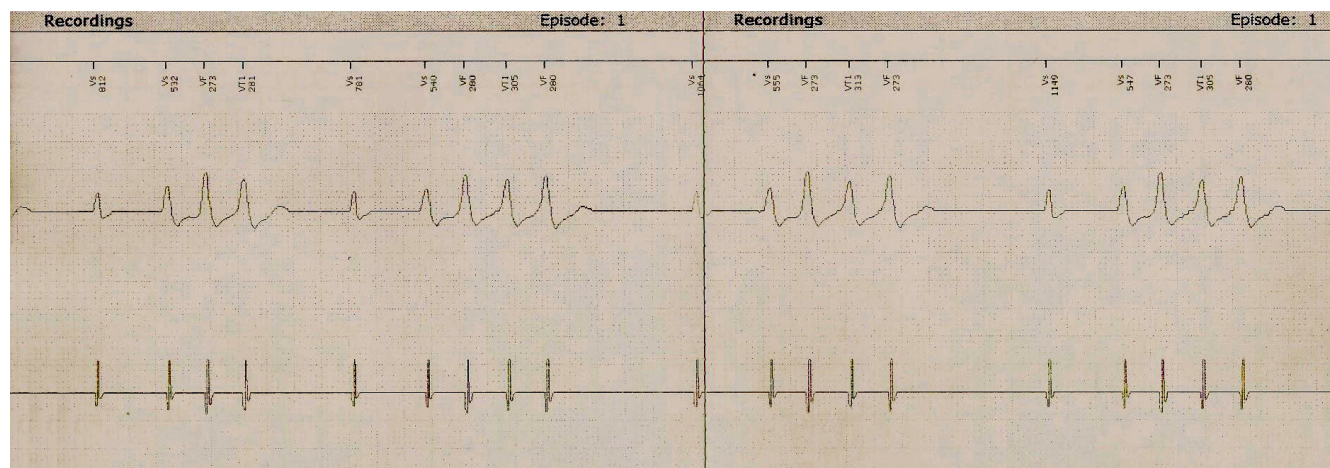
Fig. 2. The IEGM of non-sustained ventricular tachycardia (nsVT)

biostatistician (I.K.) and tested before the final implementation. The program (called PCRR) uses the same input signals as the existing ICDs with RR interval as the primary input variable. This program was created on the basis of the SAS v. 9e statistical package (SAS Institute, Cary, USA). Before the final implementation in the presented study, the use of PCRR was validated on different 36 recordings containing 4000–9890 RR intervals.

Methods

From the database containing an RR intervals series of the arrhythmia events and controls stored in ICD memory (Biotronik models Belos VR (n = 45), Phylax XM (n = 32), Lexos VR (n = 47), and Micro Phylax (n = 18)), 142 consecutive patients recordings with IEGMs were included in the analysis. The basic inclusion criterion was the presence of sinus rhythm and at least 4000 RR intervals and the corresponding IEGM, recorded 66 ±15 min before an ICD intervention or before a follow-up visit if there was no intervention. Patients with paced rhythm were not included. The 2000 PDM-Patient Data Manager software (Biotronik, Berlin, Germany) was used for data storage and graphical analysis, made independently by 2 experienced cardiologists. The RR patterns could be presented in a graphical form as a map of dots in relation to their predecessors. This method, however, is not widely used in clinical practice. All RR pattern figures presented in this paper, except the PCRR program, were produced with the 2000 PDM-Patient Data Manager. Data were collected during follow-up visits on a six-month schedule or after clinical events, whichever came first. Eleven patients were excluded due to a lack of a full dataset or due to the presence of supraventricular arrhythmias (atrial fibrillation or flutter).

This study complies with the Declaration of Helsinki and research protocol and was approved by the local ethics committee. Informed consent was obtained from all patients.

Statistics

Statistical analyses were performed using the SAS v. 9e statistical package. For descriptive purposes, all data are presented as mean ± standard deviation (SD; continuous variables) or as absolute frequencies and percentages, where indicated (discrete variables). T or χ^2 tests were used, as appropriate. All test procedures were two-sided with a p-value of less than 0.05 indicating statistical significance.

The receiver operating characteristics curve (ROC) analysis was used to determine the cut-off point value of the PVC count to predict the appropriate ICD intervention event. The optimal cut-off was defined as the value of the maximal sum of sensitivity and specificity. Comparison of the PVC ROC in the 2 models was performed on the basis of area under curve (AUC). Binary logistic regression was performed.

Results

Detailed patient characteristics (demographic data, etiology, laboratory results, major comorbidities, etc.) are presented in Table 1. The rate and the values of the phenomena defined in the study protocol are presented in Table 2.

In the overall analysis, the number of PVCs/4000 RR intervals was significantly higher in group A (263 ±32 compared to 43 ±17, p < 0.0001). The mean PVC coupling interval was significantly shorter in group A (320 ±13 compared to 400 ±38, p = 0.029). The number of PVCs of very short cycle lengths (180–220 ms) in group A and B was 1 ±0.4 compared to 0.1 ±0.1, respectively (p = 0.028). The number of PVCs of short cycle lengths (220–280 ms) in group A and B was 5 ±1.2 compared to 0.6 ±0.4, respectively (p = 0.0007). The incidence of SLS sequences was significantly higher in group A than in group B (p < 0.0001).

The percentage of patients demonstrating different cycle length intervals of PVC events appears in Fig. 3

Table 1. Patient characteristics (demographic data, etiology, laboratory results, major comorbidities, etc.)

Parameter	Study group A (n = 101)	Controls group B (n = 83)	p-value
Age [years], mean (SD)	65 (23)	41 (11)	p < 0.001
BMI [kg/m²], mean (SD)	24.5 (7.0)	21 (4.0)	p < 0.0001
Male sex, n (%)	74 (73.3)	44 (53.1)	p < 0.004
Diabetes, n (%)	55 (54.5)	28 (33.7)	p < 0.005
LVEF [%], mean (SD)	31.3 (8.2)	45.2 (9.8)	p < 0.002
CAD, n (%)	60 (59.4)	30 (36.1)	p < 0.001
MI, n (%)	50 (50)	5 (6.02)	p < 0.001
Arterial hypertension, n (%)	75 (74.3)	35 (42.2)	p < 0.001
Previous cardiac arrest, n (%)	85 (84.1)	32 (38.5)	p < 0.001
HCM (%)	18 (17.8)	14 (16.9)	NS
DCM (%)	15 (14.9)	12 (14.5)	NS
Other etiology (%)	8 (7.9)	11 (13.2)	NS
Creatinine [mg/dL], mean (SD)	1.0 (0.30)	0.85 (0.14)	NS

SD – standard deviation; NS – not significant; BMI – body mass index; LVEF – left ventricular ejection fraction; CAD – coronary artery disease; MI – myocardial infarction; HCM – hypertropic cardiomyopathy; DCM – dilated cardiomyopathy.
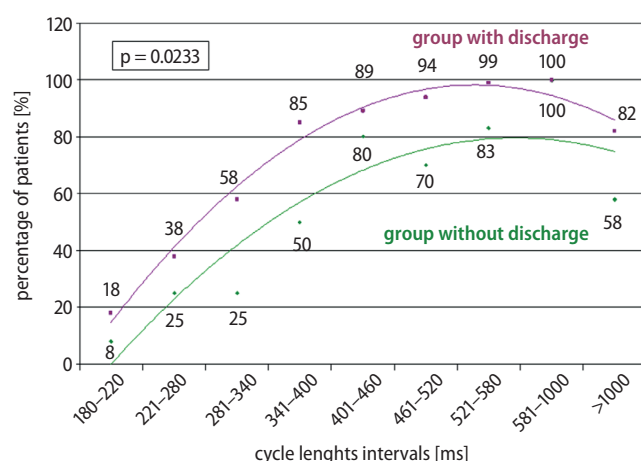
Fig. 3. Comparison of patients (%) within different cycle lengths intervals of PVC events in group A and B

Table 2. The rate and the values of the phenomena defined in the study protocol

Parameter	Group A	Group B	p-value
PVC defined as RR interval shorter >10% than the predecessor			
Mean RR of PVC (c.l.)	640 ±101	625 ±213	NS
Minimal RR of PVC (c.l.)	**314 ±112**	**400 ±132**	**0.019**
Maximal RR of PVC (c.l.)	945 ±192	896 ±190	NS
PVC number/4000 RR	**263 ±32**	**43 ±17**	**<0.0001**
PVC defined as RR interval shorter >20% than the predecessor			
Mean RR of PVC (c.l.)	**593 ±82**	**529 ±183**	**0.049**
Minimal RR of PVC (c.l.)	**320 ±112**	**400 ±132**	**0.029**
Maximal RR of PVC (c.l.)	891 ±160	828 ±146	NS
PVC number/4000 RR	**174 ±24**	**15 ±7**	**<0.0001**
Mean number of cycles			
Cl: 180–220 ms	1 ±0.4	0.1 ±0.1	0.028
Cl: 220–280 ms	5 ±1.2	0.6 ±0.4	0.0007
Cl: 280–340 ms	18 ±11	51 ±49	NS
Cl: 340–400 ms	23 ±9	16 ±15	NS
Cl: 400–460 ms	88 ±46	17 ±11	NS
Cl: 460–520 ms	126 ±79	189 ±129	NS
Cl: 520–580 ms	315 ±9	350 ±150	NS
Cl: 580–1000 ms	2870 ±134	3075 ±245	NS
Cl: 1200–2000 ms (long cycles)	523 ±134	273 ±117	NS
Mean RR interval in relation to predecessor	**45 ±37**	**19 ±13**	**<0.0001**
Incidence of short-long-short (SLS) sequence, number of patients (%)	**67 (94%)**	**4 (33%)**	**<0.001**
Couplets	45 (63%)	4 (33%)	NS
Runs of nsVT	**28 (39%)**	**1 (8%)**	**0.0490**

PVC – premature ventricular complex; NS – not significant; c.l. – cycle lengths; CI – coupling intervals. Values in bold are statistically significant.

(p = 0.0233). Graphical representation of RR interval patterns from PDM 2000 (comparing patients from group A and group B) are presented in Fig. 4.

The template presented in the upper panel in Fig. 4 would be regarded as a "risk pattern" for group A, with frequent PVCs of short coupling interval, and the lower panel would be typical for a normal, healthy heart. The upper recording comes from a 72-year-old patient after myocardial infarction, EF = 20%. During the observation period, many episodes of VT (145 bpm) with unsuccessful ATP occurred, terminated with cardioversion of 10 joules. The lower panel in Fig. 4 represents the case of a 52-year-old patient after acute myocarditis with VF in the acute phase. Initial EF after the episode was 30% and ICD was implanted. Later on, complete recovery with the improvement of EF to normal

limits and no ICD therapies in the follow-up period were observed.

Graphical representation of RR interval patterns from PDM 2000 within the same patient are presented in Fig. 5. The RR interval series presented in upper panels in Fig. 4 and 5 originated from the same patient. They are presented in such a manner for better visual comparison with lower panels. The PCRR program makes RR interval analysis possible. The results are presented above, at the beginning of the Results section. However, the program also generates graphs with RR interval distributions and corresponding PVC burden in different CI. An example of RR distribution in patients from group B (left panel) and group A (right panel), generated as a print-out created from the PCRR program, is presented in the form of a graphical abstract in Fig. 6. It summarizes the differences between PVC characteristics in a graphical form in relation to RR interval cycle length.

The ROC were created as a predictor of ICD intervention for both models described in method section (Fig. 7 below; left panel: model 1, right panel: model 2). The results of ROC comparison of statistical significance for PVC in the 2 tested models on the basis of AUC are presented in Table 3.
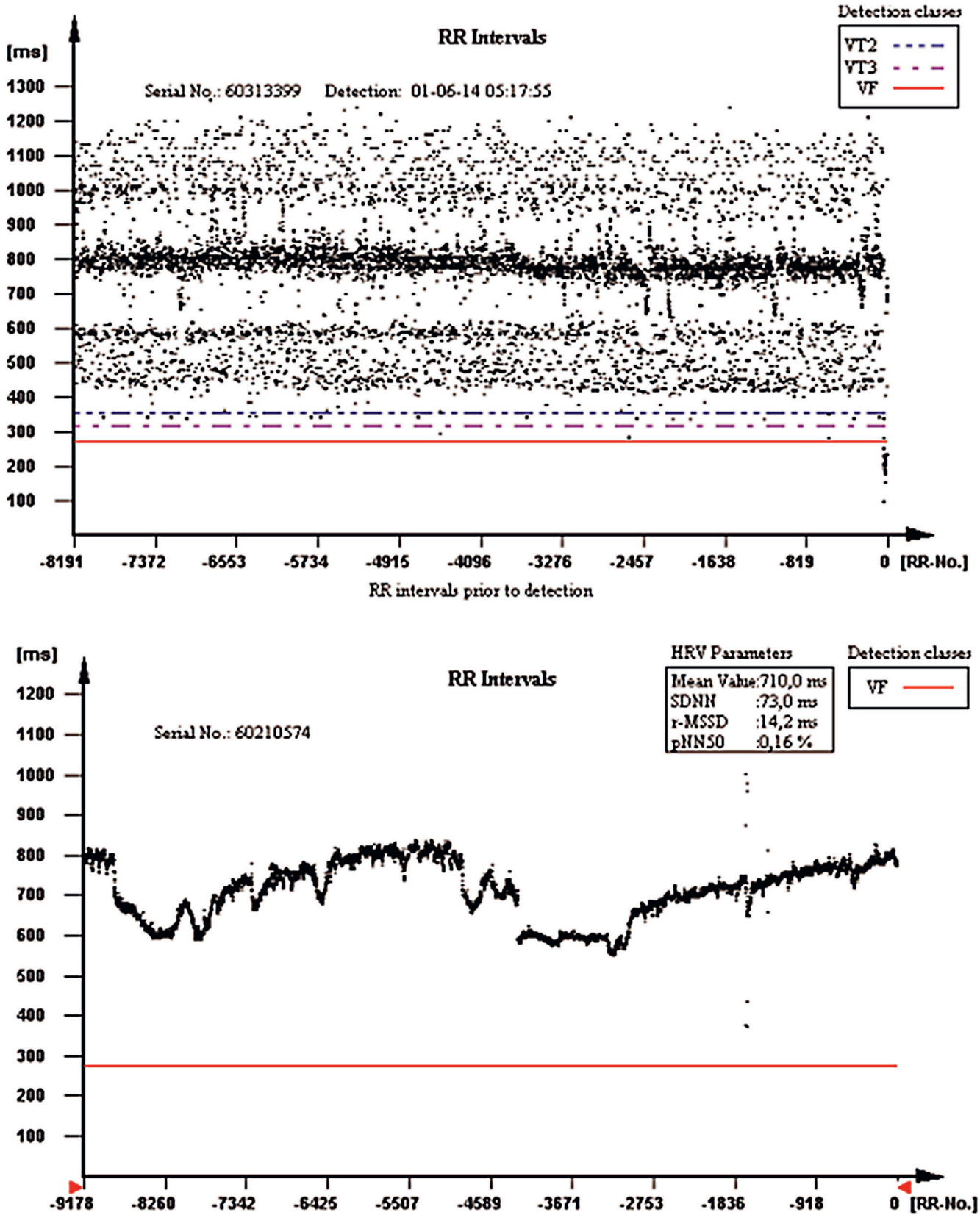
Fig. 4. Graphical differences of RR pattern from PDM 2000 (between patients from group A and group B)
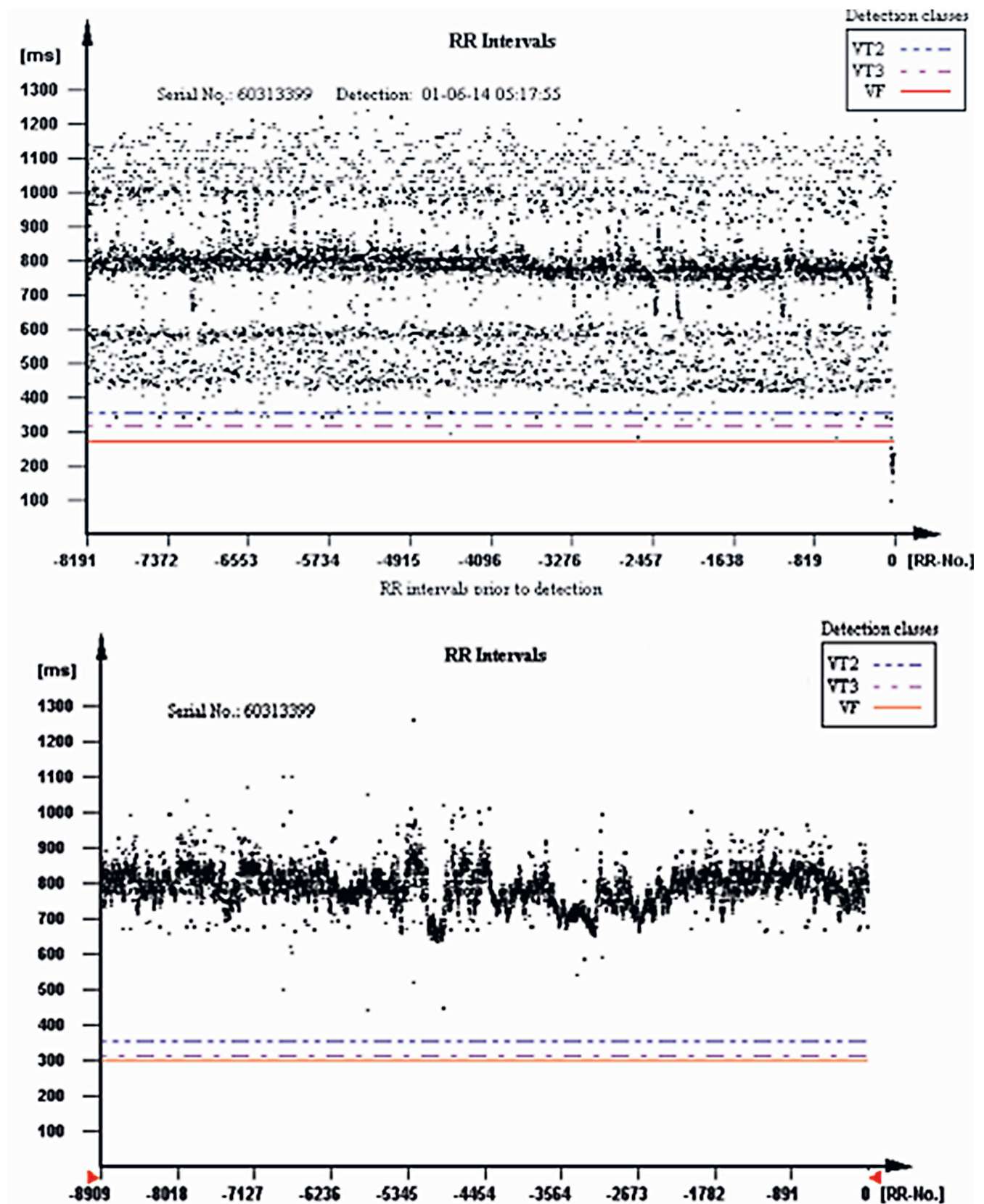
Fig. 5. Graphical differences of RR pattern from PDM 2000 within the same patient. Upper panel – RR recordings just before VF; lower panel – RR series during a routine follow-up visit without arrhythmia and no ICD intervention
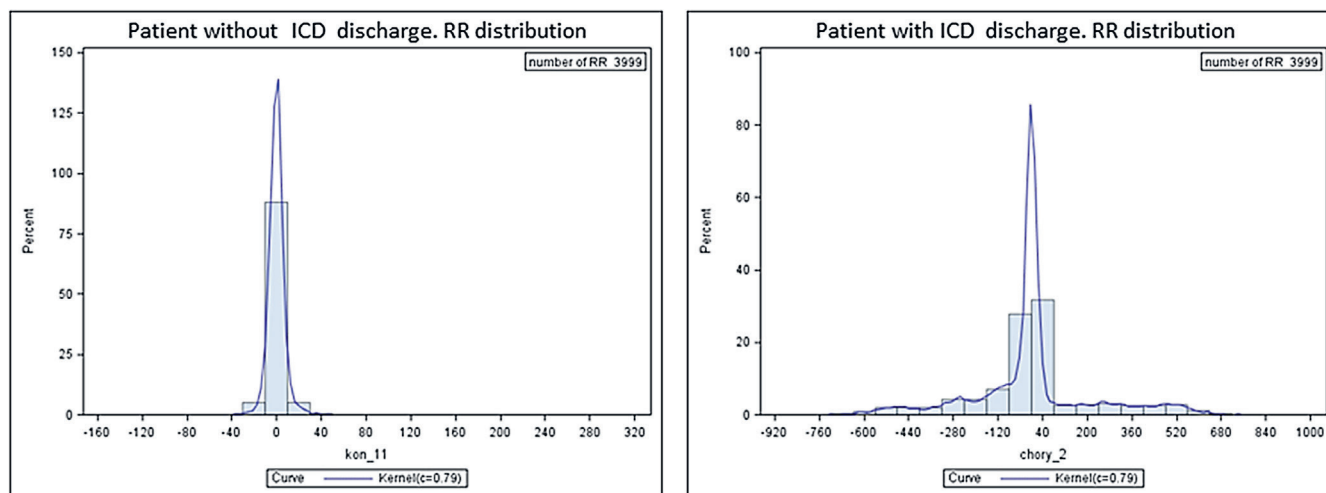
Fig. 6. Graphical differences of RR pattern from PCRR (between patients from group B and group A)
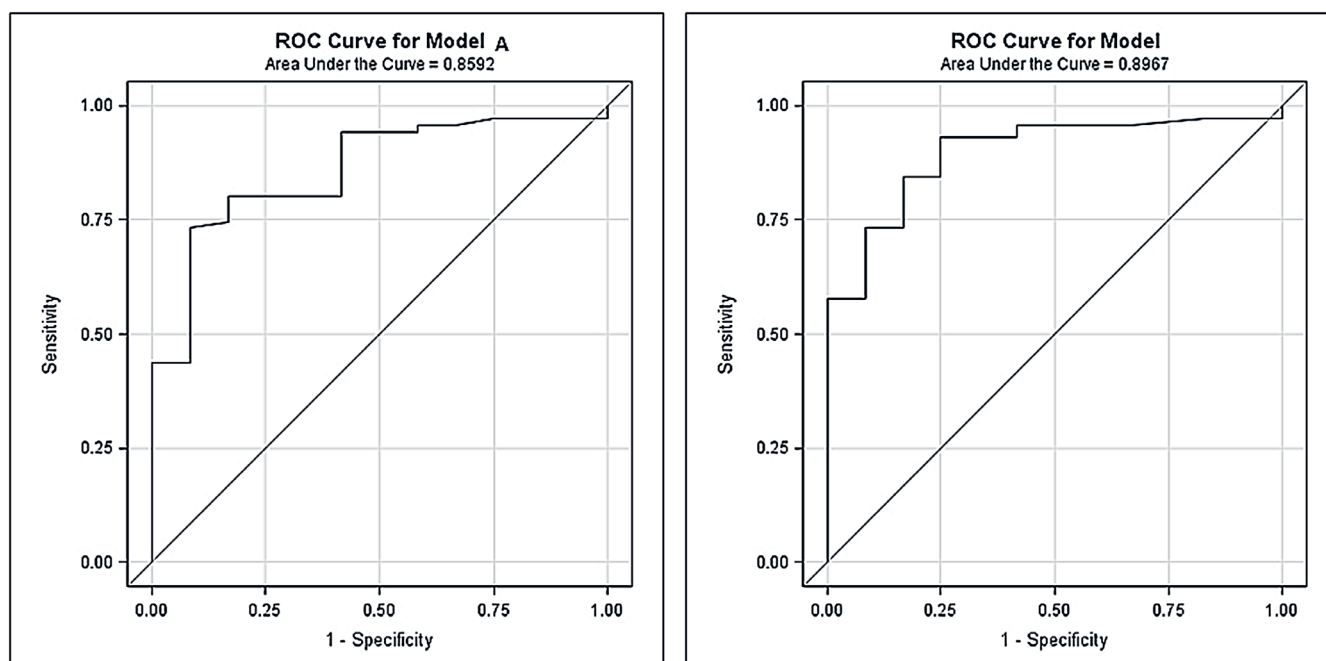

Fig. 7. ROC curves as a predictor of ICD intervention for the analyzed PVC models: 1 (left panel) and 2 (right panel)

Discussion

The mechanisms leading to VT/VF initiation are still not fully understood. In patients with CAD and heart failure (e.g., MADIT trial population), a characteristic pattern of ventricular tachyarrhythmias initiation has been recognized; namely, 77% of the episodes were initiated by PVC and 23% with an SLS sequence.[3] In this etiology, it is suggested that the Purkinje fibers are resistant to ischemia so these surviving cells surrounded by necrotic tissue demonstrate a high degree of automaticity, triggered activity and abnormal excitability.[9] It has been demonstrated that the Purkinje fibers also play a role in VF initiation in structural heart diseases such as DCM, amyloidosis and chronic myocarditis, and in hereditary syndromes without structural heart disease, such as long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia.[7,10] Two mechanisms are postulated in this situation: the triggered activity from Purkinje tissue or re-entry in the Purkinje system. On the cellular level, Ca^{2+} overload is considered as a trigger for delayed afterdepolarizations; in some cases, it can be suppressed using verapamil. There is some evidence that PVCs could trigger VF, but sometimes a PVC will precede an arrhythmia event without triggering it.[8] In some reports, idiopathic VF and polymorphic ventricular tachycardia were associated with a short-coupling interval between PVCs and conducted beats.[11] Our study is concordant with this observation. PVCs with very short and short cycle lengths (180–220 ms and 220–280 ms, respectively) were more

Table 3. Results of the ROC comparison for PVCs in 2 tested models

ROC for PVC Model 1 (left panel of Fig. 7)	
Odds ratio [95% CI], p-value for PVC number/4000 RR	2.1 [1.15–3.7]; p = 0.002
Area under the curve ROC	0.859
Sensitivity	88.7%
Specificity	58.3%
Cut-off point for ROC (number of episodes)	30
ROC for PVC Model 2 (right panel of Fig. 7)	
Odds ratio [95% CI], p-value for PVC number/4000 RR	4.7 [1.34–16.3]; p = 0.003
Area under the curve ROC	0.897
Sensitivity	88.7%
Specificity	75%
Cut-off point for ROC (number of episodes)	12

PVC – premature ventricular complex; 95% CI – 95% confidence interval; ROC – receiver operating characteristic.

frequent in patients with appropriate ICD therapy. Sanchez et al. found no significant difference between PVC coupling intervals of those that did or did not trigger VF.[8,11] Also, it was shown that the origin of PVCs is important. The PVCs originating from a peripheral Purkinje network were more likely to be present during the occurrence of electrical storm than those coming from the right ventricular outflow tract (RVOT).[9] The latter PVC could still trigger VF, albeit less frequently, as there are reports of successful radiofrequency catheter ablation of unifocal PVC of RVOT origin for recurrent VF.[11] Of course, the origin of the PVC was not in our dataset, as our data came from ICD IEGM, not from the localization technique used in electrophysiology laboratory.

The PVC ablation is considered a feasible technique and could be considered as an indication for reducing ICD shock rates and even withholding the ICD implantation decision.[12] A multicenter study followed 38 patients after PVC RFA for idiopathic VF.[7] Eighteen percent had recurrent VF and 5 were treated successfully with redo procedures of triggering PVC ablation during the five-year follow-up period. A relationship between PVC burden and left ventricular function was recognized.[13] The reported percentage of daily PVC burden (determined by 24-hour Holter monitoring), which led to the deterioration of the left ventricular systolic function (PVC-mediated cardiomyopathy), varies from 10%, through 16% and 24%, to 30%.[14] Catheter ablation techniques for PVCs have recently become successful treatment in clinical practice with a success rate >80%.[15–17] Search for different mechanisms leading to VT/VF initiation and the discussion on the organization of VF in human myocardium is still of broad and current interest.[18]

Baseline PVC assessment is important as a significant burden is associated with increased risk for SCD and total

cardiac death.[19] Screening for the presence of frequent PVCs should be part of the decision-making process in primary prophylaxis ICD implantation as trigger ablation is an effective therapy in scar-related or PVC-triggered arrhythmias. The ESC SCD Guidelines (2016) recommend catheter ablation (Class IIa, Level B) in patients with LV dysfunction, PVC burden >24% and short coupling PVC intervals (<300 ms).[20] Our findings strongly supports these recommendations and other recent reports.[21] On the basis of our pilot report on patients with ICD, we believe that the created program and the associated rate variability pattern could be a tool for prediction of SCD risk in different populations. The main advantage of the PCRR program is its low computational complexity. Its simplicity allows for either hardware implementation in a specific integrated circuit or implementation in software on standard microprocessors.

In addition, no pre-processing of the IEGM raw signal is necessary. In the past, we have shown that it is possible to transfer RR intervals recordings in a simple text format transfer, as shown on the dedicated website (http://defib.imio.pw.edu.pl/).[22] The PCRR implementation can easily make the transition to telemedicine-based practices, e.g., monitoring of ECG and implantable loop recorders.

The fact that there are still gaps in the basis of evidence for sudden cardiac death clinical predictors encouraged us to work in this field and create a new RR interval analysis program (PCRR) to question whether ventricular ectopic activity could be regarded as a predictive marker. Heart rate variability (HRV) and others have been proposed as SCD risk factors but they are not widely used due to their complexity and sophistication.

Limitations

This study is a single-center, retrospective analysis. The enrollment number is limited due to a lack of full data, i.e., an RR interval pattern with the corresponding IEGM. The study group is heterogeneous in terms of risk etiology and clinical characteristics, but the main aim of the study was to create the RR interval analysis program on the basis of a consecutive ICD patient group. For this reason, we performed an analysis of coupling intervals preceding VT/VF and controls only. It should be kept in mind that more complex trigger factors are involved in the induction of tachyarrhythmias, such as electrolyte imbalance or worsening of heart failure leading to myocardium electric instability. We were not able to compare the episodes within the same patients in all cases (e.g., device interrogations just before the therapy compared to remote from the therapy). Therefore, we compared interrogations after the therapy and during the scheduled clinical visit which was not preceded by any therapy. Some participants were treated with amiodarone, which could have affected the PVC pattern compared to those not receiving antiarrhythmic drugs. The RR interval sequences were

based on the coupling intervals and compensatory pauses. The IEGM does not enable verification of PVC morphologies. We merged ATP and ICD shocks recordings in one group intentionally to obtain a larger RR tachyarrhythmias database. The time between the ICD implantation and therapy varied from a few months to 3 years. Therefore, a further prospective and a more extensive study is needed to validate the value of the proposed methodology.

Conclusions

Significant differences were found in the characteristics of PVCs and SLS sequences in patients with appropriate ICD interventions and controls. A newly developed basic computer program called PCRR was used for RR interval analysis. The proposed program could be a new tool to assess PVC burden and arrhythmia risk in different populations.

ORCID iDs

Michał Lewandowski   https://orcid.org/0000-0002-6829-7491
Ilona Kowalik   https://orcid.org/0000-0002-8040-5109

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