International Journal of Cardiology 225 (2016) 226–233

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Quantitative analysis of ventricular ectopic beats in short-term RR interval recordings to predict imminent ventricular tachyarrhythmia

Marisol Martínez-Alanis [a,b], Silvia Ruiz-Velasco [c], Claudia Lerma [a,*]

[a] Departamento de Instrumentación Electromecánica, Instituto Nacional de Cardiología Ignacio Chávez, México, D.F. 14080, Mexico
[b] Facultad de Ingeniería, Universidad Anáhuac, Huixquilucan, Estado de México 52786, Mexico
[c] Instituto de Investigaciones en Matemáticas Aplicadas y en Sistemas, Universidad Nacional Autónoma de México, México, D.F. 04510, Mexico

ARTICLE INFO

Article history:
Received 5 April 2016
Received in revised form 27 September 2016
Accepted 29 September 2016
Available online 03 October 2016

Keywords:
Coupling interval
Implantable cardioverter defibrillator
Premature ventricular complexes
Sudden cardiac death

ABSTRACT

Background: Most approaches to predict ventricular tachyarrhythmias which are based on RR intervals consider only sinus beats, excluding premature ventricular complexes (PVCs). The method known as heartprint, which analyses PVCs and their characteristics, has prognostic value for fatal arrhythmias on long recordings of RR intervals (>70,000 beats).
Objective: To evaluate characteristics of PVCs from short term recordings (around 1000 beats) and their prognostic value for imminent sustained tachyarrhythmia.
Materials and methods: We analyzed 132 pairs of short term RR interval recordings (one before tachyarrhythmia and one control) obtained from 78 patients. Patients were classified into two groups based on the history of accelerated heart rate (HR) (HR > 90 bpm) before a tachyarrhythmia episode. Heartprint indexes, such as mean coupling interval (meanCI) and the number of occurrences of the most prevalent form of PVCs (SNIB) were calculated. The predictive value of all the indexes and of the combination of different indexes was calculated.
Results: MeanCI shorter than 482 ms and the occurrence of more repetitive arrhythmias (sNIB ≥ 2.5), had a significant prognostic value for patients with accelerated heart rate: adjusted odds ratio of 2.63 (1.33–5.17) for meanCI and 2.28 (1.20–4.33) for sNIB. Combining these indexes increases the adjusted odds ratio: 10.94 (3.89–30.80).
Conclusions: High prevalence of repeating forms of PVCs and shorter CI are potentially useful risk markers of imminent ventricular tachyarrhythmia. Knowing if a patient has history of VT/VF preceded by accelerated HR, improves the prognostic value of these risk markers.

1. Introduction

Identifying patients at risk of sudden cardiac death (SCD) is an unresolved challenge [1,2], despite many existing methods for SCD risk stratification, such as inducibility of arrhythmias [3,4], heart rate variability (HRV) and T-wave alternans [2–4]. HRV methods include only beats originated in the sinus node [5]. However, in many cases of SCD there is a high incidence of premature ventricular complexes (PVCs) before the occurrence of sustained tachyarrhythmia (VT/VF) [6,7]. Therefore, the prevalence of PVCs is also recognized as a risk factor for SCD [8–11].

This work is focused on a method known as heartprint, which is based on the representation of sinus beats and their relation to characteristics of PVCs such as the coupling interval or CI (which is time duration between a PVC and its preceding sinus beat), and the number of intervening sinus beats (NIB) between two consecutive PVCs [12]. This method has been applied in long term recordings obtained from Holter monitors to describe a pattern of ventricular bigeminy in patients with long QT syndrome and SCD that may be due to early afterdepolarizations [13]. Also, the heartprint obtained from Holter recordings of patients with myocardial infarction showed several indexes that predict SCD [14]. On the other hand, the heartprint from short term recordings has been applied to describe different patterns of ventricular ectopy before VT/VF in patients wearing an implantable cardioverter defibrillator (ICD) [15]. However, most methods to predict SCD based on short term RR interval time series obtained from ICDs are based on HRV indexes [16,17].

The aim of this work was to evaluate the predictive value of PVCs characteristics obtained with the heartprint method to predict sustained tachyarrhythmia (VT/VF) from short-term HRV recordings (~1000 heart beats).

* Corresponding author at: Departamento de Instrumentación Electromecánica, Instituto Nacional de Cardiología Ignacio Chávez, Juan Badiano No. 1. Col Sección XVI. Tlalpan, México, D.F. 14080, Mexico.
E-mail address: dr.claudialerma@gmail.com (C. Lerma).

http://dx.doi.org/10.1016/j.ijcard.2016.09.117
0167-5273/

Table 1
Clinical characteristics of patients and number of recordings per patient. Data is shown as either absolute value (percentage) or median (25 percentile–75 percentile).

	Heart rate at last minute		Tachyarrhythmia type		
	≥90 bpm (N = 58)	<90 bpm (N = 20)	VT (N = 53)	VF (N = 19)	Mixed (N = 6)
Age (years)	61 (52–67)	67 (61–71)*	63 (53–69)	61 (54–68)	55 (52–69)
Sex					
Male	47 (81%)	16 (80%)	44 (83%)	14 (74%)	5 (83%)
Female	11 (19%)	4 (20%)	9 (17%)	5 (26%)	1 (17%)
Body mass index (kg/m^2)	27 (25–29)	26 (2–29)	27 (24–29)	27 (23–31)	27 (23–29)
Diagnosis					
Myocardial infarction	37 (64%)	12 (60%)	38 (72%)	8 (42%)	3 (50%)
Congestive heart failure	24 (41%)	6 (30%)	18 (34%)	9 (47%)	3 (50%)
Dilated cardiomyopathy	20 (34%)	6 (30%)	14 (26%)	10 (53%)	2 (33%)
Others	17 (29%)	6 (30%)	6 (11%)	6 (32%)	3 (50%)
LVEF (%)	26 (20–38)	25 (18–32)	25 (20–38)	25 (15–33)	24 (15–30)
NYHA class					
I	20 (34%)	5 (25%)*	17 (32%)	6 (32%)	2 (33%)
II	31 (53%)	9 (45%)*	29 (55%)	8 (42%)	3 (50%)
III or IV	7 (12%)	6 (30%)*	7 (13%)	5 (26%)	1 (17%)
Medication					
Betablocker	22 (38%)	5 (25%)	23 (43%)	3 (16%)	1 (17%)
Digoxine	16 (28%)	7 (35%)	13 (25%)	7 (37%)	3 (50%)
Antiarrhythmic drug	18 (31%)	8 (40%)	17 (32%)	7 (37%)	2 (33%)
Others	7 (12%)	2 (10%)	7 (13%)	2 (11%)	0 (0%)
None	13 (22%)	6 (30%)	13 (25%)	5 (26%)	1 (17%)
Number of recordings per patient					
Before tachyarrhythmia	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)[&]	3(2–3)[&,#]
Total before tachyarrhythmia	104	31	97	22	16
Control	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)[&]	3 (2–3)[&,#]
Total control	104	31	97	22	16

* $p < 0.05$ compared to group with HR ≥ 90 bpm.
[&] $p < 0.05$ compared to VT group.
[#] $p < 0.05$ compared to VF group.

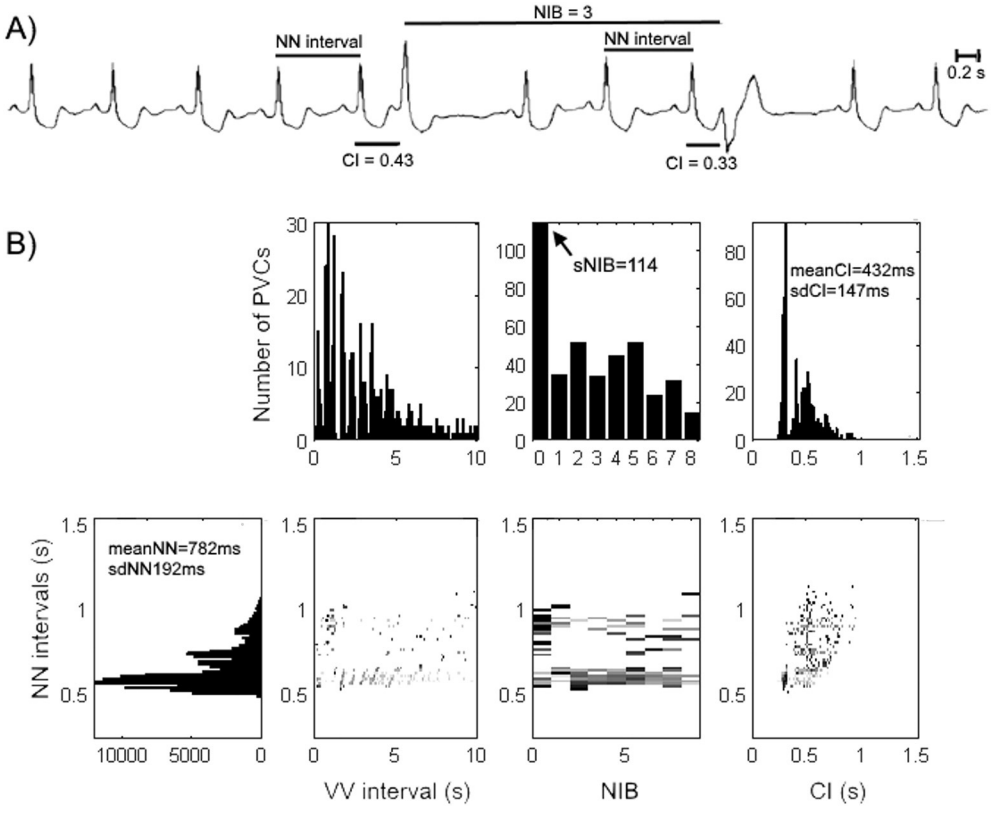

Fig. 1. Example of RR analysis with heartprint technique from recording number 30 of the Sudden Cardiac Death Holter Database to illustrate a case with variable coupling intervals. See explanation in the text.

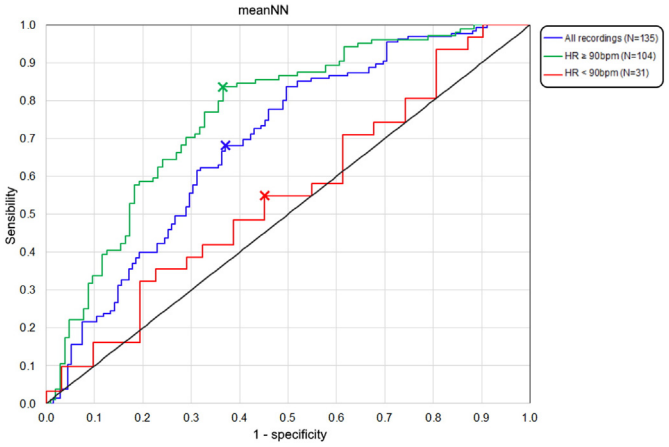

Fig. 2. Receiver-operator characteristics (ROC) curves of the mean NN interval evaluated from short-term ICD recordings before VT and control. The best cut-off value (indicated by the symbol "X") was calculated as the shortest orthogonal distance to the optimum value in the graph (0, 1).

2. Methods

2.1. Subjects and data

Data for this study were obtained from the Spontaneous Ventricular Tachyarrhythmia Database Version 1.0 from Medtronic Inc. (available at http://physionet.org/physiobank/database/mvtdb/) [18]. One hundred thirty five pairs of RR interval time series were obtained from electrograms recorded with ICDs (Medtronic Jewel PlusTM ICD 7218), each pair included one recording before VT or VF and one control recording which was obtained during a follow-up visit. Table 1 describes the clinical characteristics of the 72 patients enrolled in the study. The patients were separated into two groups according to the mean heart rate one minute prior VT/VF: (i) accelerated heart rate (mean HR ≥ 90 bpm) in at least one recording preceding VT/VF, and (ii) normal heart rate (mean HR < 90 bpm) in all recordings preceding VT/VF [19]. The group with accelerated heart rate was slightly younger and had more patients with NYHA class ≤II than the group with normal heart rate before VT/VF. All other characteristics (sex, body mass index, diagnosis, left ventricular ejection fraction and medication) were similar between groups. There were similar characteristics between patients with only VT episodes, patients with only VF episodes and the mixed group (patients with both VT and VF episodes).

2.2. Heart rate variability analysis

The RR interval time series provided by Physionet include an annotation of each beat type. However, the annotations included in the Spontaneous Ventricular Tachyarrhythmia Database are unaudited, i.e. all beats are labeled as normal (N). RR intervals from PVCs were identified by an adaptive filtering algorithm (available on the toolbox for complex systems (TOCSY) webpage: http://tocsy.agnld.uni-potsdam.de/) [20]. Each RR interval from a PVC was labeled as ventricular (V). The classification for each beat was evaluated by visual inspection in order to correct when necessary. Since estimation of HRV indexes require RR intervals from sinus origin only [5], the RR intervals from PVCs were substituted by estimated RR intervals from sinus beats to create an NN interval time series [20]. The NN interval time series were divided in five minute windows without overlap in order to calculate the mean (meanNN) and standard deviation (sdNN) [5]. The mean heart rate 1 min prior to the VT/VF episode was evaluated in the NN interval series.

2.3. Heartprint analysis

Based on the annotations of the RR interval time series, each pair of successive RR intervals was classified as NN, NV, VN or VV. The ventricular arrhythmias were classified depending on their repeating sequences as follows: bigeminy (VNV), trigeminy (VNNV) and quadrigeminy (VNNNV). The number of intervening N beats between two consecutive V beats is known as the NIB value (e.g. the NIB value for bigeminy is 1, while for quadrigeminy is 3). The coupling interval (CI) is the elapsed time between a V beat and its preceding sinus (N) beat [12,13,15]. These calculations are used to obtain the heartprint for each RR interval time series (Fig. 1). The heartprint, along with its indexes were generated using custom written Matlab software (The MathWorks, Inc., Natick, MA).

Other characteristics that were measured from the heartprint to identify potential risk factors include the average CI value (meanCI), CI standard deviation (sdCI), total ventricular ectopy (PVCs per hour) and the number of incidence of the most prevalent NIB value, known as the NIB index (sNIB) [14].

2.4. Statistical analysis

The statistical analysis was performed with the computer program IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY) and Stata version 14 using the melogit package (StataCorp, College Station, TX). Since most ordinal variables did not have a normal distribution ($p < 0.05$, Kolmogorov–Smirnov test), they are described as median (percentile 25–percentile 75). Comparisons between groups were made using either a Mann–Whitney U test (accelerated HR vs normal HR and VT vs VF) or a Wilcoxon signed-ranked test (tachyarrhythmia episode vs control). The area under the receiver operating characteristic (ROC) curve was calculated for each index. There are no established cut-off values for HRV indexes obtained from short term recordings, and heartprint indexes have been tested only in Holter recordings [14]. Therefore, the optimal cut-off value of each index was

Table 2
Heart rate variability (HRV) and *heartprint* indexes grouped by mean heart rate 1 min before the tachyarrhythmia episode (shown as median (percentile 25–percentile 75)). bpm = beats per minute.

	HR ≥ 90 bpm (N = 104)		HR < 90 bpm (N = 31)	
	Before VT/VF	Control	Before VT/VF	Control
MeanNN (ms)	655 (585–728)*	780 (704–907)	828 (745–915)&	819 (738–884)
sdNN (ms)	52 (36–79)	51 (30–78)	41 (30–66)	40 (23–76)
PVCs/h	167 (46–490)*	78 (11–346)	156 (31–307)	49 (17–397)
MeanCI (ms)	497 (405–562)*	574 (504–644)	592 (525–617)&	579 (535–623)
MeanCI/meanNN	0.752 (0.664–0.814)	0.731 (0.666–0.795)	0.714 (0.622–0.771)*	0.721 (0.668–0.792)
sdCI (ms)	56 (39–74)*	60 (43–87)	64 (42–80)	44 (30–85)
sNIB	13 (2–24)	5 (2–21)	6 (2–13)	6 (1–29)

* $p < 0.05$ (before VT/VF versus control).
& $p < 0.05$ (HR ≥ 90 bpm versus HR < 90 bpm).

Table 3
Heart rate variability (HRV) and *heartprint* indexes grouped by type of tachyarrhythmia (shown as median (percentile 25–percentile 75)). bpm = beats per minute.

	VT (N = 106)		VF (N = 29)	
	Before tachyarrhythmia	Control	Before tachyarrhythmia	Control
MeanNN (ms)	689 (588–806)*	806 (715–912)	649 (586–816)*	752 (702–850)
sdNN (ms)	49 (33–76)	49 (27–72)	53 (37–77)	56 (31–82)
PVCs/h	170 (48–412)*	92 (11–351)	79 (25–675)*	52 (11–340)
MeanCI (ms)	531 (456–596)*	593 (519–649)	499 (418–616)*	548 (500–582)
MeanCI/meanNN	758 (679–818)	730 (666–796)	724 (692–776)	686 (616–768)
sdCI (ms)	62 (44–78)	56 (41–83)	63 (54–77)	61 (33–93)
sNIB	9 (3–23)	5 (1–21)	21 (4–79)	3 (1–27)

* $p < 0.05$ (before tachyarrhythmia versus control).

identified as the shortest orthogonal distance between the pair of values (1 – specificity, sensitivity) and the optimum value (0, 1) in the ROC curve (Fig. 2).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each index. The indexes with a significant value ($p < 0.05$) for the area under the ROC curve were combined in pairs, and their sensitivity and specificity was compared against the individual indexes using the McNemmar test. Finally, the odds ratio was calculated for each individual index and the index combinations using mixed effects logistic regression models adjusted by age, sex, body mass index, diagnosis, left ventricular ejection fraction (LVEF), NYHA class, medication, and type of tachyarrhythmia episode. The patient was selected as a variable with random effect while all other variables were considered as fixed effects. A value of $p < 0.05$ was considered statistically significant.

3. Results

Table 2 shows the HRV and heartprint indexes grouped according to mean HR in the last minute before VT/VF. The group with accelerated HR had a shorter meanNN and meanCI, a higher number of PVCs per hour and a more fixed CI before VT/VF compared to control recordings (indicated with *). In contrast, the group with normal HR only had a shorter meanCI/meanNN before VT/VF versus control recordings. Compared to the accelerated HR group, the group with normal HR had a higher value for both meanNN and meanCI before VT/VF (indicated with &).

Table 3 shows the HRV and heartprint indexes grouped according to tachyarrhythmia episode (VT or VF). Both groups showed that having a faster heart rate, a higher number of PVCs per hour and a shorter coupling interval can work as an indicator of the presence of a tachyarrhythmia episode compared to control. However, when comparing both groups (VT and VF) there was no significant difference for any index.

Table 4 shows the ROC curve analysis for each index considering all records, the group with accelerated HR, and the group with normal HR. The area under the ROC curve was statistically significant for four indexes: meanNN, PVCs per hour, meanCI and sNIB, in both the group including all records and the accelerated HR group. There was no index that presented a prognostic value for the group with normal HR. The area under the ROC curve of recordings before VT remained significant in meanNN, PVCs per hour and meanCI, while recordings before VF had significant area under the ROC curve in meanNN only (Table 4).

The predictive values for each index based on their optimal cut-off value are shown in Table 5. When comparing these results with a previous study that reported cut-off values for 24 h recordings [14], sensitivity and specificity values were similar, but there was a lower NPV and a higher PPV.

Based on the optimum cut-off values, the odds ratio was calculated for the different indexes, considering all records and separating by accelerated and normal HR (Fig. 3). For the group including all recordings, two indexes were independent risk factors: meanNN, 3.43 (1.80–6.53)

Table 4
ROC curve analysis for individual HRV and *heartprint* indexes.

	AUC (95% C.I.)	p	Best cut-off value	Distance to optimum value (0,1)
All records (N = 135)				
meanNN (ms)	0.691 (0.628–0.754)	<0.001	728	0.488
sdNN (ms)	0.464 (0.395–0.533)	0.311	54	0.680
PVCs/h	0.586 (0.518–0.654)	0.014	71.409	0.583
meanCI (ms)	0.582 (0.514–0.651)	0.019	534	0.602
sdCI (ms)	0.547 (0.478–0.616)	0.182	48	0.623
meanCI/meanNN	0.551 (0.482–0.620)	0.144	0.7	0.625
sNIB	0.576 (0.508–0.645)	0.030	1.5	0.716
Heart rate ≥ 90 bpm (N = 104)				
meanNN (ms)	0.764 (0.699–0.829)	<0.001	678	0.400
sdNN (ms)	0.542 (0.463–0.620)	0.301	40	0.658
PVCs/h	0.603 (0.526–0.680)	0.010	71.409	0.582
meanCI (ms)	0.607 (0.529–0.685)	0.008	482	0.571
sdCI (ms)	0.523 (0.444–0.603)	0.561	52	0.660
meanCI/meanNN	0.571 (0.493–0.649)	0.076	0.7	0.613
sNIB	0.599 (0.522–0.676)	0.013	0.5	0.717
Heart rate < 90 bpm (N = 31)				
meanNN (ms)	0.552 (0.407–0.696)	0.486	823	0.639
sdNN (ms)	0.534 (0.387–0.681)	0.647	41	0.616
PVCs/h	0.531 (0.383–0.678)	0.678	55.297	0.555
meanCI (ms)	0.543 (0.398–0.688)	0.559	587	0.616
sdCI (ms)	0.623 (0.480–0.767)	0.095	49	0.484
meanCI/meanNN	0.483 (0.336–0.629)	0.816	0.7	0.621
sNIB	0.495 (0.346–0.643)	0.944	1.5	0.665
VT (N = 106)				
meanNN (ms)	0.709 (0.639–0.778)	0.000	757	0.462
sdNN (ms)	0.539 (0.462–0.617)	0.322	41	0.638
PVCs/h	0.582 (0.505–0.660)	0.038	130.858	0.587
meanCI (ms)	0.601 (0.524–0.678)	0.011	534	0.588
sdCI (ms)	0.539 (0.461–0.617)	0.324	55	0.628
meanCI/meanNN	0.550 (0.472–0.627)	0.212	0.742	0.607
sNIB	0.568 (0.491–0.646)	0.809	2.5	0.599
VF (N = 29)				
meanNN (ms)	0.698 (0.556–0.840)	0.010	664	0.404
sdNN (ms)	0.516 (0.365–0.667)	0.834	46	0.662
PVCs/h	0.611 (0.465–0.758)	0.146	59.166	0.513
meanCI (ms)	0.526 (0.374–0.678)	0.732	500	0.585
sdCI (ms)	0.573 (0.421–0.725)	0.339	40	0.556
meanCI/meanNN	0.628 (0.483–0.772)	0.095	0.689	0.513
sNIB	0.596 (0.448–0.745)	0.208	3.5	0.536

AUC = Area under the curve, C.I. = confidence interval, bpm = beats per minute.

Table 5
Predictive values for individual HRV and *heartprint* indexes. All values are presented as percentage (95% confidence interval).

	Sensitivity	Specificity	PPV	NPV
	All records (N = 135)			
meanNN ≤ 728 ms	63 (55–71)	68 (60–76)	66 (58–75)	65 (57–73)
sdNN ≤ 54 ms	57 (49–65)	47 (38–55)	52 (44–60)	52 (43–61)
PVCs/h ≥ 71.41	68 (60–76)	51 (43–60)	58 (51–66)	62 (53–71)
meanCI ≤ 534 ms	63 (55–71)	53 (44–61)	57 (49–65)	59 (50–67)
sdCI ≤ 48 ms	38 (30–46)	51 (43–60)	44 (35–53)	45 (37–53)
meanCI/meanNN ≤ 0.040	13 (7–18)	82 (75–88)	41 (26–55)	48 (42–55)
sNIB ≥ 2.5	67 (59–75)	52 (43–60)	58 (50–66)	61 (52–70)
Heart rate ≥ 90 bpm (N = 104)				
meanNN ≤ 678 ms	63 (54–73)	84 (77–91)	80 (71–88)	70 (62–78)
sdNN ≤ 40 ms	32 (23–41)	58 (48–67)	43 (32–54)	46 (37–54)
PVCs/h ≥ 71.41	70 (61–79)	50 (40–60)	58 (50–67)	63 (52–73)
meanCI ≤ 482 ms	54 (44–63)	66 (57–75)	62 (52–72)	59 (50–68)
sdCI ≤ 52 ms	45 (36–55)	49 (39–59)	47 (37–57)	47 (38–57)
meanCI/meanNN ≤ 0.040	13 (6–19)	79 (71–87)	37 (21–53)	47 (40–55)
sNIB ≥ 2.5	67 (58–76)	53 (42–62)	59 (50–68)	62 (52–72)
Heart rate < 90 bpm (N = 31)				
meanNN ≤ 823 ms	45 (28–63)	45 (28–63)	45 (28–63)	45 (28–63)
sdNN ≤ 41 ms	55 (37–72)	45 (28–63)	50 (33–67)	50 (31–69)
PVCs/h ≥ 55.30	68 (51–84)	55 (37–72)	60 (44–76)	63 (45–81)
meanCI ≤ 587 ms	45 (28–63)	42 (25–59)	44 (27–61)	43 (26–61)
sdCI ≥ 49 ms	71 (55–87)	61 (44–78)	65 (49–81)	68 (51–85)
meanCI/meanNN ≤ 0.046	13 (1–25)	90 (80–101)	57 (20–94)	51 (38–64)
sNIB ≥ 1.5	71 (55–87)	48 (31–66)	58 (42–74)	63 (43–82)
VT (N = 106)				
meanNN ≤ 757 ms	69 (60–78)	65 (56–74)	66 (58–75)	68 (59–77)
sdNN ≤ 41 ms	38 (29–47)	53 (43–62)	44 (34–55)	46 (37–55)
PVCs/h ≥ 130.86	59 (50–69)	58 (48–67)	58 (49–68)	59 (49–68)
meanCI ≤ 534 ms	61 (52–71)	56 (46–65)	58 (49–67)	59 (49–69)
sdCI ≤ 55 ms	47 (38–57)	42 (33–52)	45 (36–54)	45 (35–54)
meanCI/meanNN ≤ 0.792	74 (65–82)	23 (15–31)	49 (41–56)	46 (33–60)
sNIB ≥ 2.5	67 (58–76)	50 (40–60)	57 (49–66)	60 (50–70)
VF (N = 29)				
meanNN ≤ 664 ms	62 (44–80)	86 (74–99)	82 (66–98)	69 (54–84)
sdNN ≤ 90 ms	41 (23–59)	52 (34–70)	46 (27–65)	47 (30–64)
PVCs/h ≥ 59.17	66 (48–83)	62 (44–80)	63 (46–81)	64 (47–82)
meanCI ≤ 500 ms	62 (44–80)	55 (37–73)	58 (41–75)	59 (41–78)
sdCI ≤ 40 ms	28 (11–44)	48 (30–66)	35 (15–54)	40 (24–56)
meanCI/meanNN ≤ 0.689	34 (17–52)	38 (20–56)	36 (18–53)	37 (19–54)
sNIB ≥ 3.5	62 (44–80)	62 (44–80)	62 (44–80)	62 (44–80)

PPV = positive predictive value, NPV = negative predictive value, bpm = beats per minute.

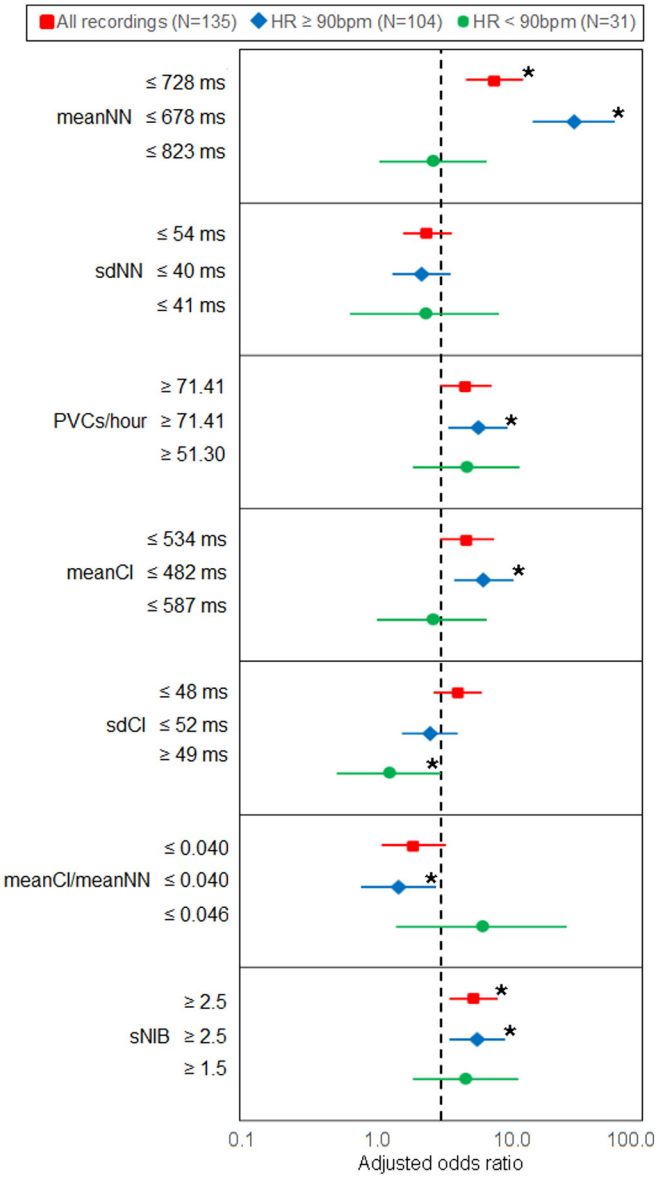

Fig. 3. Odds ratio of characteristics of PVCs evaluated from RR intervals of ICD recordings before VT/VF and control. Each odds ratio includes a 95% confidence interval and was adjusted by age, sex, body mass index, myocardial infarction, congestive heart failure, left ventricular ejection fraction, NYHA class, medication, and type of tachyarrhythmia using a mixed effect logistic regression. The patient was chosen as the random effect variable. The cut-off values selected for the calculations are presented in Table 4.

and sNIB, 2.11 (1.22–3.62). In patients with accelerated heart rate, four of these indexes proved to be an independent risk factor: meanNN, 20.86 (8.24–52.82); PVCs/h, 2.32 (1.19–4.54); meanCI, 2.63 (1.33–5.17); and sNIB, 2.28 (1.20–4.33). However, in the group with normal HR, only the index sdCI ≥49 ms had a significant odds ratio of 0.30 (0.09–0.99).

In comparison with the indexes with significant odds ratio, the combination of two indexes notably increased the odds ratio values for both the group containing all records and even more on the group with accelerated HR. However, there was no improvement in the group with normal HR (Fig. 4).

Table 6 shows that the combined indexes had lower sensitivity but higher specificity than the individual indexes.

4. Discussion

This work demonstrates that several characteristics from PVCs (e.g. having a more fixed CI or a higher number of PVCs per hour) can be used as risk factors for imminent tachyarrhythmia in short-term recordings obtained from ICDs. Combinations of these indexes in pairs increased their predictive value. The prognostic value of the indexes is independent from the clinical factors that are usually associated with the presence of tachyarrhythmia. Moreover, such prognostic value increases when it is known that a patient has a history of accelerated heart rate before a tachyarrhythmia episode. The predictive values of these indexes were similar for both types of tachyarrhythmia (VT and VF).

Previous works have proposed the evaluation of several characteristics obtained from RR intervals of patients with ICDs to predict the occurrence of tachyarrhythmias [15,17,21,22]. Among the characteristics that are solely based on sinus beats (NN interval), the one that has reported a prognostic value is meanNN, which decreases before a VT/VF episode [21,23]. This finding was confirmed in the present study when considering all recordings or those with accelerated HR, but did not occur in recordings with normal HR before VT/VF. Regarding the indexes that include RR intervals from PVCs, other works have proposed that an increased number of PVCs can be reflected in a higher risk of mortality or adverse events [8,9,11,14]. The present study also observed higher number of PVCs/h before VT/VF than in control recordings.

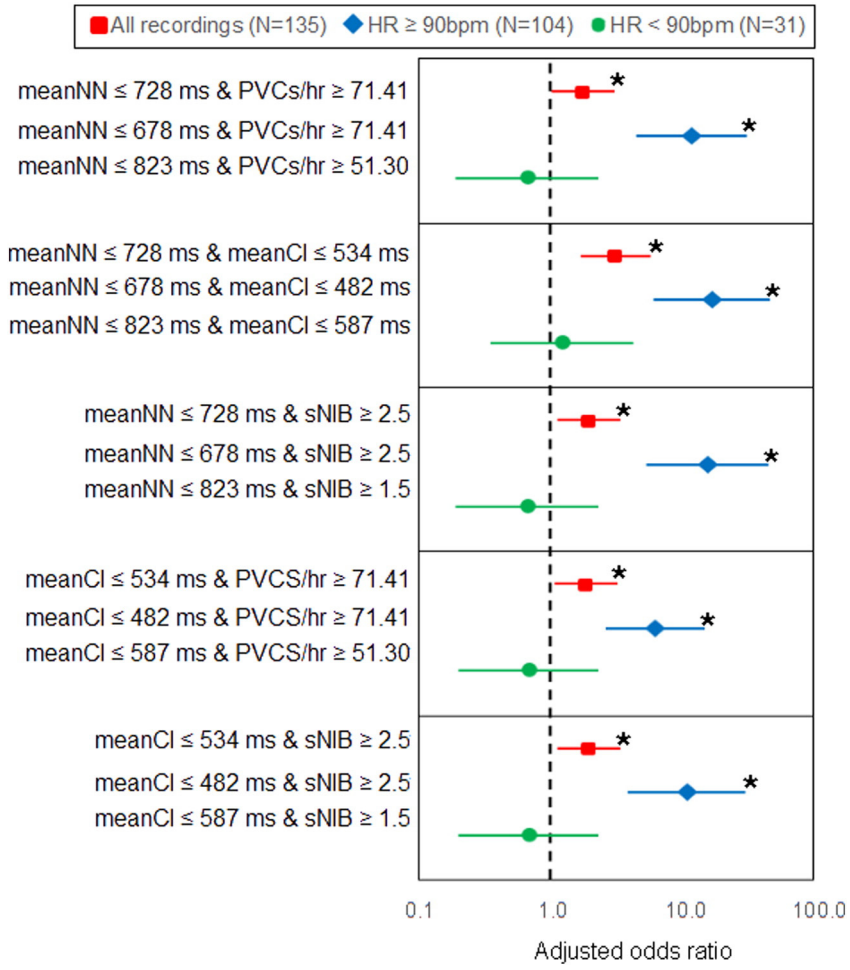

Fig. 4. Odds ratio characteristics for the combination of PVC characteristics evaluated from RR intervals of ICD recording before VT/VF and control. Each odds ratio includes a 95% confidence interval and was adjusted by age, sex, body mass index, myocardial infarction, congestive heart failure, left ventricular ejection fraction, NYHA class, medication, and type of tachyarrhythmia using a mixed effect logistic regression. The patient was chosen as the random effect variable. The cut-off values for each of the indexes in the combinations are shown in Table 4.

Table 6
Sensitivity and specificity for combined indexes. All values are presented as percentage (95% confidence interval). bpm = beats per minute.

	Sensitivity	Specificity
	All records (N = 135)	
meanNN ≤ 728 ms and PVCs/h ≥ 71.41	45 (37–54)*,&	82 (76–89)*,&
meanNN ≤ 728 ms and meanCI ≤ 534 ms	51 (43–60)*,#	76 (68–83)*,#
meanNN ≤ 728 ms and sNIB ≥ 2.5	41 (33–50)*	85 (79–91)*
meanCI ≤ 534 ms and PVCS/h ≥ 71.41	41 (33–50)&,#	78 (71–85)&,#
meanCI ≤ 534 ms and sNIB ≥ 2.5	39 (30–47)#	79 (72–86)#
	Heart rate ≥ 90 bpm (N = 104)	
meanNN ≤ 678 ms and PVCs/h ≥ 71.41	43 (34–53)*,&	93 (88–98)*,&
meanNN ≤ 678 ms and meanCI ≤ 482 ms	45 (36–55)*,#	90 (85–96)*,#
meanNN ≤ 678 ms and sNIB ≥ 2.5	40 (31–50)*	94 (90–99)*
meanCI ≤ 482 ms and PVCS/h ≥ 71.41	37 (27–46)&,#	91 (86–97)&,#
meanCI ≤ 482 ms and sNIB ≥ 2.5	35 (25–44)#	94 (90–99)#
	Heart rate < 90 bpm (N = 31)	
meanNN ≤ 823 ms and PVCs/h ≥ 51.30	35 (19–52)&	68 (51–84)*
meanNN ≤ 823 ms and meanCI ≤ 587 ms	32 (16–49)	61 (44–78)#
meanNN ≤ 823 ms and sNIB ≥ 1.5	35 (19–52)	65 (48–81)*
meanCI ≤ 587 ms and PVCS/h ≥ 51.30	29 (13–45)&	68 (51–84)#
meanCI ≤ 587 ms and sNIB ≥ 1.5	29 (13–45)	65 (48–81)#

$p < 0.05$ compared to sNIB.
* $p < 0.05$ compared to meanNN.
& $p < 0.05$ compared to PVCs/h.
\# $p < 0.05$ compared to meanCI.

In a previous study based on the analysis of the heartprint for RR intervals obtained from ICDs, there were no characteristics that showed a significant difference between control time-series and those occurring before a VT/VF episode. However, the heartprint analysis in this study was mainly qualitative [15]. The quantitative characteristics that are evaluated in this work had been previously analyzed in long-term recordings (i.e. 24-h recordings) and some of them demonstrated a prognostic value for potentially fatal arrhythmias, SCD or overall mortality in a two-year follow-up [14,24]. Even if some of the indexes that presented a prognostic value in the previous study with long term time series also have predictive value for tachyarrhythmia, the cut-off values used in this work are necessarily different given the smaller amount of available data from short term time series. Also, the population of study for the present work has clinical characteristics that are more heterogeneous than in the previous study [14]. Therefore, this work extends previous findings of patterns of arrhythmia as risk factors of SCD.

Accelerated HR as a risk factor for SCD has been widely documented using 24-h recordings [4,25] and short-term recordings obtained from ICDs [15]. Accelerated HR is usually linked to chronic sympathetic hyperactivity or to transitory sympathetic activation [26,27]. The knowledge of a history of accelerated HR could be useful for the adjustment of pharmacological treatments (e.g. with the use of beta-blockers), particularly if other characteristics, such as repetitive arrhythmias (i.e. high sNIB) or short CI (i.e. low CI) are concomitant. However, a prospective study is needed to test this hypothesis, since this work showed no

difference between the accelerated HR and normal HR groups with the use of beta-blockers or other pharmacological treatments.

Although it has not been widely studied, the sdCI has also been considered as a risk factor for cardiac death [14,23,28]. These results agree with our findings for the group with accelerated HR, in which patients with a tachyarrhythmia episode showed less variability in the CI. However, other works have reported that patients with coronary artery disease, left ventricular systolic dysfunction or non-sustained VT present a higher mortality when they have a higher variability of the CI [23,28]. The variability of the CI can also be associated with the different mechanisms of PVC occurrence: an altered conduction velocity, a PVC exiting from multiple reentrant circuits or even the nonreentrant mechanisms have shown a high CI variability [12,13,29,30].

The indexes presented in this work were obtained from patients with ICDs, which allowed us to verify the incidence of the expected outcome (i.e. ventricular tachyarrhythmia). However, the heartprint indexes presented here could also be tested as predictors of tachyarrhythmia and other cardiac events using an implantable cardiac monitor [31], as predictors of mortality in patients at the intensive care unit [32] and as predictors of cardiac arrest in the emergency department [33].

Determining the cut-off value for heartprint and HRV indexes may be useful in clinical practice to identify patients that are at risk of suffering imminent tachyarrhythmia when recordings with at least 1000 beats are available. If a patient has a fast heart rate (meanNN ≤ 728 ms), a higher number of PVCs per hour (PVCS/h ≥ 71), a shorter coupling interval (meanCI ≤ 534 ms) or a more repetitive form of arrhythmia (sNIB ≥ 2.5), there is a higher risk for this patient to develop imminent tachyarrhythmia. When two of these characteristics are concurrent, the risk of imminent tachyarrhythmia increases even further. The predictive value of these characteristics is particularly high for patients with a history of accelerated heart rate before a tachyarrhythmia episode.

4.1. Limitations

The number of records used for this work is relatively low, particularly in the group with normal HR. It is necessary to use the heartprint analysis for records obtained from an ICD in a larger sample to confirm and extend the present results. Beat classification from RR intervals was carried out using an algorithm that has been validated in previous works and is very efficient in most cases [15]. However, when the time series presents a high number of complex or repetitive arrhythmias, the algorithm becomes less efficient and requires manual correction. It is necessary to enhance the classification method in order to guarantee the best performance that will not preclude a future implementation of an automatic heartprint analysis.

There was no available information about the way each tachyarrhythmia episode was terminated (either self-terminated or interrupted by the ICD) or regarding other co-morbidities such as diabetes mellitus. Further studies are required to assess the impact of such co-morbidities on the HRV and heartprint indexes as risk markers for sudden cardiac death.

5. Conclusions

High prevalence of repeating forms of PVCs and shorter CI are potentially useful risk markers of imminent ventricular tachyarrhythmia. Knowing if a patient has history of VT/VF preceded by accelerated HR improves the prognostic value of these risk markers.

Conflict of interest

C.L. holds a patent in the subject matter.

Acknowledgements

The authors thank Leon Glass for helpful suggestions.

References

[1] J.J. Goldberger, M.E. Cain, S.H. Hohnloser, A.H. Kadish, B.P. Knight, M.S. Lauer, et al., American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention, Circulation 118 (2008) 1497–1518.
[2] C. Lerma, L. Glass, Predicting the risk of sudden cardiac death, J. Physiol. 594 (2016) 2445–2458.
[3] H.V. Huikuri, A. Castellanos, R.J. Myerburg, Sudden death due to cardiac arrhythmias, N. Engl. J. Med. 345 (2001) 1473–1482.
[4] H.J. Wellens, P.J. Schwartz, F.W. Lindemans, A.E. Buxton, J.J. Goldberger, S.H. Hohnloser, et al., Risk stratification for sudden cardiac death: current status and challenges for the future, Eur. Heart J. 35 (2014) 1642–1651.
[5] 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, Eur. Heart J. 17 (1996) 354–381.
[6] J. Bluzhas, D. Lukshiene, Ventricular tachycardia in myocardial infarction: relation to heart rate and premature ventricular contractions, Eur. Heart J. 6 (1985) 745–750.
[7] S. Viskin, S.R. Alla, H.V. Barron, K. Heller, L. Saxon, I. Kitzis, et al., Mode of onset of torsade de pointes in congenital long QT syndrome, J. Am. Coll. Cardiol. 28 (1996) 1262–1268.
[8] J.W. Dukes, T.A. Dewland, E. Vittinghoff, M.C. Mandyam, S.R. Heckbert, D.S. Siscovick, et al., Ventricular ectopy as a predictor of heart failure and death, J. Am. Coll. Cardiol. 66 (2015) 101–109.
[9] G. Ephrem, M. Levine, P. Friedmann, P. Schweitzer, The prognostic significance of frequency and morphology of premature ventricular complexes during ambulatory holter monitoring, Ann. Noninvasive. Electrocardiol. 18 (2013) 118–125.
[10] C.M. Pratt, P. Theroux, D. Slymen, A. Riordan-Bennett, D. Morisette, A. Galloway, et al., Spontaneous variability of ventricular arrhythmias in patients at increased risk for sudden death after acute myocardial infarction: consecutive ambulatory electrocardiographic recordings of 88 patients, Am. J. Cardiol. 59 (1987) 278–283.
[11] Z.I. Carrim, A.A. Khan, Mean frequency of premature ventricular complexes as predictor of malignant ventricular arrhythmias, Mt Sinai J. Med. 72 (2005) 374–380.
[12] V. Schulte-Frohlinde, Y. Ashkenazy, A.L. Goldberger, P.C. Ivanov, M. Costa, A. Morley-Davies, et al., Complex patterns of abnormal heartbeats, Phys. Rev. E. Stat. Nonlin. Soft. Matter Phys. 66 (2002) (031901–1–031901-12).
[13] C. Lerma, C.F. Lee, L. Glass, A.L. Goldberger, The rule of bigeminy revisited: analysis in sudden cardiac death syndrome, J. Electrocardiol. 40 (2007) 78–88.
[14] C. Lerma, A. Gorelick, R.N. Ghanem, L. Glass, H.V. Huikuri, Patterns of ectopy leading to increased risk of fatal or near-fatal cardiac arrhythmia in patients with depressed left ventricular function after an acute myocardial infarction, Europace 15 (2013) 1304–1312.
[15] C. Lerma, N. Wessel, A. Schirdewan, J. Kurths, L. Glass, Ventricular arrhythmias and changes in heart rate preceding ventricular tachycardia in patients with an implantable cardioverter defibrillator, Med. Biol. Eng Comput. 46 (2008) 715–727.
[16] G. Kheder, A. Kachouri, M. Samet, HRV analysis using wavelet package transform and least square support vector machine, Int. J. Circuits Syst. Signal Process. 2 (2008) 18–25.
[17] S. Joo, K.J. Choi, S.J. Huh, Prediction of spontaneous ventricular tachyarrhythmia by an artificial neural network using parameters gleaned from short-term heart rate variability, Expert Syst. Appl. 39 (2012) 3862–3866.
[18] A.L. Goldberger, L.A. Amaral, L. Glass, J.M. Hausdorff, P.C. Ivanov, R.G. Mark, et al., PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals, Circulation 101 (2000) E215–E220.
[19] A.G. Shaper, G. Wannamethee, P.W. Macfarlane, M. Walker, Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men, Br. Heart J. 70 (1993) 49–55.
[20] N. Wessel, A. Voss, H. Malberg, C. Ziehmann, H.U. Voss, A. Schirdewan, et al., Nonlinear analysis of complex phenomena in cardiological data, Herzschr Elektrophys 11 (2000) 159–173.
[21] U. Meyerfeldt, N. Wessel, H. Schutt, D. Selbig, A. Schumann, A. Voss, et al., Heart rate variability before the onset of ventricular tachycardia: differences between slow and fast arrhythmias, Int. J. Cardiol. 84 (2002) 141–151.
[22] H.V. Huikuri, D.V. Exner, K.M. Kavanagh, S.G. Aggarwal, L.B. Mitchell, M.D. Messier, et al., Attenuated recovery of heart rate turbulence early after myocardial infarction identifies patients at high risk for fatal or near-fatal arrhythmic events, Heart Rhythm. 7 (2010) 229–235.
[23] M. Sosnowski, J. Skrzypek-Wanha, B. Korzeniowska, M. Tendera, Increased variability of the coupling interval of premature ventricular beats may help to identify high-risk patients with coronary artery disease, Int. J. Cardiol. 94 (2004) 53–59.
[24] H.V. Huikuri, M.J. Raatikainen, R. Moerch-Joergensen, J. Hartikainen, V. Virtanen, J. Boland, et al., Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction, Eur. Heart J. 30 (2009) 689–698.
[25] E.Z. Soliman, M.A. Elsalam, Y. Li, The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording, Europace 12 (2010) 261–265.

[26] K. Fukuda, H. Kanazawa, Y. Aizawa, J.L. Ardell, K. Shivkumar, Cardiac innervation and sudden cardiac death, Circ. Res. 116 (2015) 2005–2019.
[27] M.J. Shen, D.P. Zipes, Role of the autonomic nervous system in modulating cardiac arrhythmias, Circ. Res. 114 (2014) 1004–1021.
[28] C.H. Lee, K.H. Park, J.H. Nam, J. Lee, Y.J. Choi, E.J. Kong, et al., Increased variability of the coupling interval of premature ventricular contractions as a predictor of cardiac mortality in patients with left ventricular dysfunction, Circ. J. 79 (2015) 2360–2366.
[29] T. Maruyama, M. Fukata, Increased coupling interval variability — mechanistic, diagnostic and prognostic implication of premature ventricular contractions and underlying heart diseases, Circ. J. 79 (2015) 2317–2319.
[30] L. Glass, A.L. Goldberger, J. Belair, Dynamics of pure parasystole, Am. J. Phys. 251 (1986) H841–H847.
[31] P.E. Bloch Thomsen, C. Jons, M.J. Raatikainen, J.R. Moerch, J. Hartikainen, V. Virtanen, et al., Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study, Circulation 122 (2010) 1258–1264.
[32] M.K. Moridani, S.K. Setarehdan, A.M. Nasrabadi, E. Hajinasrollah, New algorithm of mortality risk prediction for cardiovascular patients admitted in intensive care unit, Int. J. Clin. Exp. Med. 8 (2015) 8916–8926.
[33] M.E. Ong, C.H. Lee Ng, K. Goh, N. Liu, Z.X. Koh, N. Shahidah, et al., Prediction of cardiac arrest in critically ill patients presenting to the emergency department using a machine learning score incorporating heart rate variability compared with the modified early warning score, Crit. Care 16 (2012) R108.