Peak Ectopy Rate Analysis for Risk Stratification of Sudden Death in Heart Failure

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Abstract

Aim of this paper is to propose a new parameter, based on 24-hour holter recording, that quantifies abnormal ventricular activity by calculating the peak ectopic rate (PEAK_ER) of every patient.

This parameter is tested on a population of 200 heart failure (HF) patients in sinus rhythm (age (median [interquartile range]): 54 years [47-58], ejection fraction (EF): 23% [19-28]. During the 5 year follow-up 23 patients suddenly died. Classification obtained from PEAK_ER is compared with that from left ventricular ejection fraction (EF), non-sustained ventricular tachyarrhythmias (NSVT) and premature ventricular contractions per hour (PVC/h). We also considered combinations of PEAK_ER, NSVT and PVC/h with EF. End-points are total cardiac death (CD) and sudden cardiac death (SCD). Performances are assessed by total accuracy, sensitivity and specificity.

On both end-points EF alone reaches best sensitivity and worst specificity; Peak_ER alone performs better than NSVT and slightly better than PVC/h; EF+Peak_ER performs on average slighly better than EF+NSVT and EF+PVC/h.

In conclusion, results from present study indicate that investigation of time course of arrhythmic events may improve identification of patients with HF at increased risk of arrhythmic sudden death.

1. Introduction

Sudden death accounts for one-third to one-half of all deaths in patients with chronic heart failure (CHF) [1]. Prophylactic implantable cardioverter defibrillator (ICD) therapy has been shown to improve overall survival in patients with symptomatic heart failure and reduced left ventricular ejection fraction (EF) resulting from both coronary as well non-coronary disease [2,3]. ICD implantation is suggested, as primary prevention, in cardiac patients with EF$\leq$30% [2]. However, the identification of patients at risk solely based on EF still remains a controversial issue [4], supporting the need for a further attempt to improve the identification process. Furthermore, although many studies in the 1970s reported that the presence of frequent premature ventricular contractions (PVCs) and left ventricular systolic dysfunction carried an increased risk for sudden cardiac death among post-myocardial infarction patients, counting PVCs from Holter recording has gained less popularity in the setting of heart failure because of conflicting results. While in some studies [5,6] the frequency of PVCs showed a significant association with sudden death or major arrhythmic events only in univariate analysis, it showed an independent predictive value in others [7]. This inconsistency in results might be explained observing that NSVT considers only runs of tachycardic events and the PVCs/h parameter provided by Holter systems gives only an average rate of occurrence of arrhythmic events during the 24-hour, being the same in patients in whom a given number of ectopies occurs scattered over time and in patients in whom the occurrence is concentrated within short periods of time. No indices related to time course of arrhythmic events has been proposed up to now. We hypothesized that this information would be relevant in determining the risk of sudden death in heart failure patients. To test this hypothesis we developed a new index based on the measurement of the peak rate of ectopies occurring in a Holter recording, and investigated its prognostic value in a population of mild-to-moderate CHF patients.

2. Methods

2.1. Data set

We considered 200 mild-to-moderate CHF patients in sinus rhythm and stable clinical conditions (no changes in signs, symptoms or therapy in the 2 weeks preceding the study) admitted to the Heart Failure Unit of the Scientific Institute of Montescano between 1992 and 1996 for evaluation and treatment of heart failure. The study was

approved by the local ethics committee and all patients gave their informed consent.

All patients underwent standard clinical and laboratory examinations within one week from the Holter recording. Patients were periodically re-evaluated and eventually readmitted to hospital during the follow-up period. NSVT was defined as 3 or more consecutive ventricular premature beats at a rate > 100 beats/min that were not sustained for more than 30 seconds. Deaths were accurately investigated by chart review or telephone interview of relatives or referring physician and the date and modality (progressive heart failure, sudden or other causes) were entered into a dedicated database together with clinical data. Death was considered sudden (presumably arrhythmic) if it occurred i) within 1 hour of onset of symptoms in a previously clinically stable patient, ii) during sleep or iii) within 1 hour of the patient last being seen alive in an unwitnessed situation.

Holter recordings were performed using a two-channel recorder and processed using a Synetec System (ElaMedical). Each beat was first automatically labeled as normal or aberrant by the Holter analysis software and then carefully edited by an expert analyst. In this study Holter recordings are analysed retrospectively, then they are correlated to major events (cardiac death or sudden cardiac death).

2.2. Parameters of classification

Using an automated procedure, the 24-hour recording was entirely scanned shifting a 30 beat window one beat at a time. In each window the number of ventricular ectopic beats is computed and the maximum value found in the overall recording is taken as the parameter representative of that patient. This parameter is named peak ectopy rate (PEAK_ER). This index is compared with principal indices specifically derived from the occurrence of ectopic beats: presence of non sustained VT (NSVT) and premature ventricular contraction per hour (PVC/h). Moreover we considered the ejection fraction (EF) which is nowadays the most used parameter for risk stratification [2, 3].

2.3. Statistical analysis

Continuous data are presented with their median value and their inter-quartile range (range between 25^{th} and 75^{th} percentiles). The predictive value of studied parameters was assessed by total accuracy (Acc), sensitivity (Sens) and specificity (Spec).

The definition of thresholds (when a single parameter is considered) and separation-equations (when 2 parameters are combined) are discussed here. These values influence sensitivity and specificity estimations and we chose them on the basis of clinical considerations. In particular, the threshold for EF% (th_{EF}=30) is chosen considering that a left ventricular ejection fraction EF%$\leq$30% indicates high risk of death [2]. Similarly $th_{PVC/h}$=10 is chosen because PVC/h$\geq$10 was associated with higher mortality rates in a study of prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction [8]. Finally it is known that the presence of runs of NSVT on 24-hour ambulatory electrocardiogram predicts major arrhythmic events in patients with idiopathic dilated cardiomyopathy [9]; thus we defined as threshold th_{NSVT}=1. Threshold for the peak ectopic rate had to be set without information from the literature. Heuristic considerations led us to assume th_{PEAK_ER}=6 as the threshold of Peak_ER.

Classification with 2 parameters is supported by the idea that EF, on the one hand, and NSVT, PVC/h or Peak_ER, on the other hand, have independent prognostic values. This may also have a physiological correlate: while left ventricular ejection fraction quantifies hemodynamic cardiac performances, PVC/h, NSVT or Peak_ER are used to quantify frequency and severity of cardiac arrhythmias. Thus the classification plane is constructed considering as x-value the EF of that patient, while y-value is its Peak_ER (or PVC/h or NSVT). To define a separation line we observed that it is known from the literature [10] that risk stratification based on EF≤30% alone has high sensitivity and very poor specificity; so we accepted that "low-risk group" could have EF $\leq$ 30, and we made the "physiological assumption" that, when PVC/h = 0 or Peak_ER = 0 or in the absence of NSVT, EF would never be lower than 20%. With these conditions, the line separating low- and high-risk patients is described by:

$$PVC/h = 8.33 * EF - 175.0 \quad (1)$$

$$Peak\_ER = 1.76 * EF - 35.3 \quad (2)$$

In case of combined EF+NSVT the logical condition used to define patients at high risk is:

$$(\text{Not NSVT}) \;\&\; EF \leq 23 \;\; OR \;\; NSVT \;\&\; EF \leq 32. \quad (3)$$

When a classifying point occurs above the -separation line (i.e., the patient has higher PVC/h or higher Peak_ER or runs of NSVT), the corresponding patient is classified as "high risk"; on the contrary, when it occurs below the line, the patients is classified as "low risk".

3. Results

Demographic and clinical characteristics of the study patients are given in table 1.

End-points of the study are total cardiac death (*CD*) and sudden cardiac death (*SCD*). *CD group* includes 94 patients (47% of the total population) who died during the

5 year follow-up (median: 31 months, interquartile range: 12-60) because of: heart failure, SCD, myocardial infarction, or they needed ICD therapy or received heart transplant status 1, while *SCD group* includes 23 patients (11.5 % of total population). SCD is assessed following description in sub-section 2.1.

Results of the classification for every end-point are presented considering single parameters (EF, PVC/h, NSVT or Peak_ER alone) and then considering the combination of EF with Peak_ER (PVC/h, NSVT) to test the improvement that could be achieved by classifying groups with two parameters.

Table 1. Demographic and clinical characteristics of studied patients (N=200); Data expressed as median (25^{th} percentile, 75^{th} percentile). NYHA: New York Heart Association; other parameters defined in the text.

Demographic	
Age, yrs	54 (47,58)
Male, %	87
Clinical	
NYHA Class II-III, %	88
Etiology Cardiomyopathy	
Ischemic, %	50
Idiopathic, %	45
Echocardiographic	
EF, %	23 (19,28)
Holter	
PVC/h, n	13 (3,47)
NSVT, %	37
PEAK_ER, n	6 (3,11)
Therapy	
ACE-inhibitors/AT_1	
Receptor antagonist, %	91
Diuretics, %	96
Nitrates, %	56
Digoxin, %	77
β-blockers, %	13
Amiodarone, %	28

The same thresholds, line separations and logical function are used for the classifications with both end-points. Table 2 reports major results.

4. Discussion and conclusions

Despite a large number of studies have developed several prognostic models for assessing individual risk in heart failure, the identification of patients who could benefit from more aggressive treatment, including the ICD implantation, is still a challenging task. In this study we propose a novel index measuring the maximum rate of ectopies occurring in a 30 beats window during a 24-hour Holter recording, and investigate its prognostic power in relation to sudden death in a population of mild-to-moderate HF patients.

Table 2. Results expressed in terms of total accuracy, sensitivity and specificity.

	Parameter	Acc	Sens	Spec
Cardiac Death (94 patients)	EF	54	91	21
	PVC/h	55	63	48
	NSVT	55	41	67
	Peak_ER	58	65	52
	EF+PVC/h	62	70	54
	EF+NSVT	59	77	42
	EF+Peak_ER	64	73	55
Sudden Cardiac Death (23 patients)	EF	24	87	15
	PVC/h	47	65	44
	NSVT	60	35	63
	Peak_ER	51	78	47
	EF+PVC/h	49	78	45
	EF+NSVT	39	74	34
	EF+Peak_ER	48	78	44

Results of Table 2 show that the best sensitivity performances are obtained with EF parameter alone (91% with end-point total cardiac mortality, and 87 with end-point sudden cardiac death). EF also has the worst specificity (21% with end-point total cardiac mortality, and 15% with end-point sudden cardiac death) and total accuracy. This result is consistent with previous results from the literature [10] showing that with MADIT II specifications an average of 18 patients need to be treated (thus receive an ICD) to prevent 1 premature death in 2 years. Indeed this fact has opened up a debate on cost-effectiveness of the risk stratification based on EF alone [4].

Total accuracy is higher with Peak_ER than EF (see Table 2). The combination of EF with Peak_ER improves total accuracy with CD end-point. The analysis of Peak_ER alone with end-point SCD reaches interesting performances: 78% sensitivity and 47% specificity. We note that the combination EF+Peak_ER does not improve performances because of the *physiological assumption* that a patient with EF $\leq$ 20 could not be classified at low-risk of SCD, while in this data base many of the patients with EF $\leq$ 20 did not die for SCD.

Comparison between classifications obtained using Peak_ER, PVC/h or presence of NSVT indicates that Peak_ER alone achieves better sensitivity than the others with both end-points. Combination of EF with Peak_ER, PVC/h or NSVT evidence on average slightly better results using EF+Peak_ER: with the SCD end-point NSVT+EF give worst performances, while practically no differences are observed between EF+PVC/h and EF+Peak_ER, while with end-point CD best total accuracy and specificity are obtained with EF+Peak_ER,

although EF+NSVT reached a slightly higher sensitivity.

In Figure 1 an example of classification plane constructed to separate SCD group (indicated with '*') from others (indicated with 'o') is shown; in this example the classification is performed using EF+Peak_ER parameters. In the figure, as decribed before, points lying in the upper semi-plane are assumed to be patients with high risk of sudden death, while points below the line separation are assumed to be derived from patients with lower SCD risk. Better performances could be achieved with different choices of line-separation-equations, but interpretation would not be reasonable.

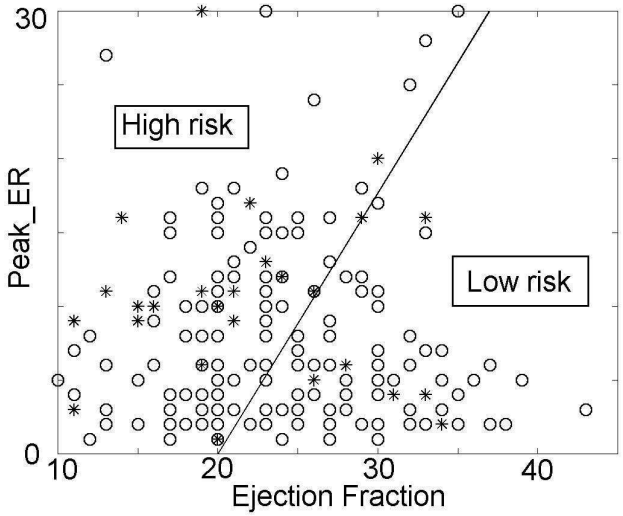

Figure 1: Plot of the classification planes for the analyses of *SCD* (indicated as '*') vs. *Other* (indicated as 'o' populations using EF and Peak_ER parameters

The present study has some limitations that deserve to be addressed. The first limitation is the relatively small sample size of the study (200 patients), with only 23 sudden deaths. The other critical point is the low portion of patients treated with beta-blockers (13.5%).

In conclusion, the results from the present study indicate that the investigation of the time course of arrhythmic events may improve the identification of patients at increased risk of sudden death and prompts towards including the assessment of short-term ectopy rate in future studies designed to appraise treatment decision in HF patients.

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