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Original Article

Predictive role of heart rate turbulence in ischemic cardiomyopathy patients with frequent implantable cardioverter defibrillator (ICD) shock therapy

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Abstract: Recent studies have revealed that patients with left ventricular (LV) dysfunction are associated with increased risk of mortality and implantable cardioverter defibrillator (ICD) shock therapy. We assessed holter parameters including presence of nonsustained ventricular tachycardia (NSVT), heart rate variability (HRV), heart rate turbulence (HRT) parameters named Turbulence onset (TO) and Turbulence slope (TS) in ischemic cardiomyopathy (IC) patients with frequent ICD shocks. Methods: We prospectively enrolled 60 IC patients with ICD shock therapy. Both NSVT, HRV, HRT were evaluated by using ambulatory Holter monitoring. HRT was considered positive when both TO and TS were abnormal (TO ≥ 0% and TS ≤ 2.5 ms/RR interval. Results: 6 patients were not utilized because of frequent ventricular premature beats (VPB) unable to be computed, 4 were lost to follow-up. Of 50, 25 (50%) had ≥ 3 ICD shock therapy. Frequent ICD shocks were not related to gender, hypertension, diabetes, renal dysfunction, hypercholesterolemia, and medical therapy (P > 0.05). Age > 65 years, NSVT, number of VPB, ≥ 2 Lown grade VBP, TS and a TO outcome were significantly associated with frequent ICD therapy (P=0.023, P=0.021, P=0.007, P=0.011, P=0.015, respectively). In multivariate analysis presence of NSVT and turbulence slope ≤ 2.5 ms/RR interval were independent predictors of frequent ICD shocks (OR 4, 19 [95% CI 1.164-15.105] P=0.028 and 3.98 [95% CI 1.137-13.970] P=0.031), respectively. Conclusion: Our study reveals that presence of NSVT and abnormal TS can predict frequent ICD shocks in IC patients. However, further investigations with larger populations are needed to get more accurate results.

Keywords: Heart rate turbulence, implantable cardiac defibrillator shock therapy, ischemic cardiomyopathy

Introduction

Life-threatening ventricular arrhythmias are more common cause of sudden cardiac death (SCD) in patients with ischemic origin of systolic heart failure (HF) [1]. Current guidelines recommend implantable cardioverter-defibrillators (ICDs) for treatment of ventricular tachyarrhythmias and prevention of SCD in heart failure [2]. In addition to measurement of ejection fraction, other risk stratification methods have being investigated.

Recently, nonsustained ventricular tachycardia (NSVT) on Holter electrocardiogram (ECG) [3, 4], microvolt T-wave alternans [5], heart rate variability [6], and sustained ventricular tachyarrhythmias (VTs) in electrophysiologic testing [7, 8] have been used to determine cardiac mortality risk in patients with reduced left ventricular ejection fraction (LVEF).

Heart rate turbulence (HRT) has been defined as a noninvasive prognostic method to reveal the cardiac death risk in high risk patients. This method shows short-term fluctuations of RR intervals following ventricular premature beats (VPBs) [9]. Under normal conditions, there is short acceleration with subsequent deceleration of heart rate following VPBs. In high risk patients this typical biphasic HRT response is

Table 1. Baseline characteristics of study patients

Clinical Features	Total (n=50) n (%)
Age (years)	64±9
Gender (male/female)	43 (86)/7 (14)
LVEF%	26.2±5.4
Hypertension	40 (80)
Diabetes	17 (34)
Hypercholesterolemia	26 (52)
Renal dysfunction	23 (46)
ICD (primer/seconder)	15 (30)/35 (70)
ICD shock number (per day)	3±2

LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator.

blunted or entirely missing. And it is believed to show baroreflex sensitivity.

We assessed HRT parameters in ischemic cardiomyopathy (IC) patients with frequent ICD shocks to reveal its prognostic power over other risk prediction methods.

Methods

Between January 2011 and December 2012 we prospectively enrolled 50 (43 men and 7 women; mean age 64±9 years) IC patients (mean LVEF 26±6%). Who were hospitalized after documented episodes of appropriate ICD shock therapy. Patients had received an ICD for primary (15 patients, 30 percent) or secondary (35 patients, 70 percent) prevention. Clinical characteristics and demographic features of patients are listed in **Table 1**. Informed consent was obtained from each patient. The study was approved by the Ethics Committee of our institute. Exclusion criteria were as follows: nonsinus rhythm (atrial fibrillation, paced rhythm), reversible causes of ventricular arrhythmic events, nonischemic causes consisted of idiopathic dilated cardiomyopathy (DCM), cardiac resynchronization therapy (biventricular pacing), or if they were in the acute phase of congestive heart failure or MI.

İschemic cardiomyopathy defined as echocardiographic left ventricular dysfunction (left ventricular ejection fraction ≤ 35 to 40 percent) with any of the following were stenosis of a major coronary artery of ≥ 75% on angiography, documented previous myocardial infarction, a history of percutaneous coronary revascularization, and a history of coronary artery bypass graft surgery [10].

Echocardiography was performed with an echocardiography platform (GE Vivid 3, GE Healthcare, Piscataway, New Jersey, USA) equipped with a 1.5-3.6 MHz phased-array probe. LVEF was calculated using biplane Simpson method from apical four-chamber and two chamber views [11].

Appropriate ICD therapy was defined as an antitachycardia pacing or shock therapy for ventricular tachycardia or fibrillation. Three or more appropriate shocks were accepted as frequent ICD shock therapy. Inappropriate shocks were excluded from the study.

Holter electrocardiography, heart rate variability, heart rate turbulance

In hospital settings, all patients underwent 12-leads 24-hours ambulatory ECG monitoring by using DMS 300-3 M diagnostic monitoring system recorders after they were clinically stabilized. Recordings were analyzed by CARDIO SCAN software (V12.0; DMS Holter Stateside, USA) by expert cardiologist. The presence of VPB and NSVT were assessed. NSVT was defined as 3 or more consecutive beats arising below the atrioventricular node with an RR interval of < 600 ms (> 100 beats/min) and lasting < 30 s. VPB grading was determined by Lown grading system and grades 2 to 5 were defined frequent and complex VPB [12, 13].

Time- and frequency-domain parameters of HRV were automatically calculated and standard deviation of RR intervals of all normal beats (SDNN) was chosen as the measure of HRV and SDNN < 70 msn was determined abnormal [14].

ECG recordings with eligible VPB, a single VPB with neighboring 20 RR intervals free of artifacts ,were processed by software algorithm for automatic analysis of HRT parameters including turbulence onset (TO) and turbulence slope (TS) which were described as an expression of early acceleration and late deceleration respectively [9, 15].

Turbulence onset was measured as percentage change between the mean of first two RR intervals after a ventricular premature beat (RR1

Table 2. Comparison of risk variables between frequent ICD shock and non-frequent ICD shock patients

	Total (n=50) n (%)	ICD calc < 3 shock (n=25) n (%)	ICD calc ≥ 3 shock (n=25) n (%)	*P* value
Age ≥ 65 years	25 (50)	8 (32)	17 (40)	0.023
LVEF%	26.2±5.4	27.6±5.6	24.6 ±4.9	0.04
VPB number	3764±6172	1677±3979	6878±7558	0.007
Lown class ≥ 2VPB	26 (52)	9 (36)	17 (68)	0.046
NSVT	21 (42)	6 (24)	15 (71)	0.021
HRVSDNN (ms)	84.3±32	88.9±28.5	75.3±34.9	0.09
TO (%)	-0.04±2.2	-1.1±2.1	0.2±2.1	0.015
Tslope (ms/RR interval)	4.4±4.8	6.5±5.8	2.2±1.7	0.011
TO ≥ 0%	26 (52)	9 (36)	17 (68)	0.04
TS ≤ 2.5 ms/RR interval	25 (50)	8 (32)	17 (68)	0.023
HRT positive	18 (36)	4 (32)	14 (56)	0.07
Medical Treatment				
Beta-blockers	37 (74)	17 (68)	20 (80)	0.52
ACE inhibitors/ARB	26 (52)	13 (52)	13 (52)	1.00
Statins	28 (56)	12 (48)	16 (64)	0.39
Class III antiarrhythmic drugs	21 (42)	9 (36)	12 (48)	0.56

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HRT, heart rate turbulence; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; VPB, ventricular premature beat; SDNN, standard deviation of all normal RR intervals; TO, turbulence onset; TS, turbulence slope.

and RR2) and the two last RR intervals before VPB (RR-1 and RR-2), using the formula: [(RR1 + RR2) - (RR-1 + RR-2)]/(RR-1 + RR-2) × 100. Turbulence slope was measured as the maximum positive slope of among all slopes in a series of regression lines obtained from five consecutive RR intervals within the first 15 sinus beats after the VPC, and expressed in ms/RR interval [9, 16]. TO and TS were dichotomized at predefined cut points (TO=0%, TS=2.5 ms/RR interval). Patients were defined as HRT positive when both TO and TS were abnormal (TO ≥ 0% and TS ≤ 2.5 ms/RR interval), and as HRT negative when TO and/or TS were normal (TO < 0% and/or TS > 2.5 ms/RR interval).

Statistical analysis

Statistical analyses were performed using SPSS software version 16 (SPSS Inc. Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk test). To determine whether or not they are normally distributed. Descriptive analyses were presented using mean ± standard deviation for normally distributed variables. Ordinal variables were presented as number of cases with percentage. Continuous variables were compared between frequent ICD shock and non-frequent ICD shock patients were evaluated by Mann-Whitney Test and categorical variables were compared by chi-square test in the non-parametric cases. While investigating the association between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the spearman test. For the multivariate analysis the possible factors identified with univariate analyses were further entered into the binary logistic regression analysis with backward selection method to find the potential predictors of frequent ICD therapy after device implantation. Hosmer-Leme show goodness of fit statistics was used to assess model fit. A 5% type-I error level was used to infer statistical significance.

Results

Of 60 patients were enrolled in the study, 6 were not utilized because very frequent VPBs unable to be computed, 4 were lost to follow-up. Statistical analysis was conducted 50 IC

Table 3. Risk variables associated with frequent ICD shock therapy in ischemic cardiomyopathy patients: backward multivariate logistic regression analysis

	OR	95% CI	P
NSVT	4.193	1.164-15.105	0.028
TS ≤ 2.5 ms/RR interval	3.985	1.137-13.970	0.031

NSVT: nonsustained ventricular tachycardia; TS: Turbulence slope. Other variables did not retain in the model to predict frequent ICD shock therapy: Turbulance Onset, Abnormal SDNN, Lown class ≥ 2 VPB. OR, Odds Ratio; CI, confidence interval.

patients (43 men and 7 women; mean age 64±9 years) (mean LVEF 26±6%) with appropriate ICD shock therapy (3±2 shock/day). Comparison of risk variables of frequent ICD shock and non-frequent ICD shock patients were presented in **Table 2**. NSVT, VPB frequency, LVEF, SDNN, HRT, TO, and TS were compared between groups.

Average values for TO and TS were -0.04±2.2% and 4.4±4.8 ms/RR interval respectively. HRT was determined as abnormal in 18 patients (36%) and normal in 32 patients (64%). The average HRVSDNN was 84.36±32.02 ms. NSVT was documented on Holter ECGs in 21 patients (42%), mean VPB number was 3764± 6172.

In univariate analysis, there were no significant differences among two groups in gender, hypertension (HT), diabetes mellitus (DM), renal dysfunction, hypercholesterolemia, and adjuvant medications such as aspirin, beta-blockers, statins, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and class III antiarrhythmic drugs, (P > 0.05) between groups. LVEF, age > 65 years, documentation of NSVT, number of VPB, ≥ 2 Lown grade VBP, TS and a TO outcome were found significantly different between frequent ICD shock and non-frequent ICD shock groups (P=0.04, P=0.023, P=0.021, P=0.007, P=0.011, P=0.015, respectively). SDNN did not get statistical significance (P=0.89).

A multivariate logistic regression analysis was conducted for univariate noninvasive risk predictors (Lown class ≥ 2 VPB, SDNN < 70 ms, TO ≥ 0%, TS ≤ 2.5 ms/RR interval and NSVT) to define the potential predictors of frequent ICD therapy in ischemic cardiomyopathy patients. NSVT and abnormal TS were the only independent predictors of frequent ICD therapy in multivariate logistic regression analysis with comparable odds ratios 4.19 (95% CI 1.164-15.105 P=0.028) and 3.98 (95% CI 1.137-13.970, P=0,031), respectively (**Table 3**).

Discussion

Our study focused on the predictive value of holter parameters especially HRT for frequent ICD shocks in patients with LV dysfunction. HRT was evaluated with other risk markers of mortality as left ventricular ejection fraction, number and class of VBP, NSVT and heart rate variability.

Reduced left ventricular ejection fraction has been shown as predictor of sudden cardiac death and total mortality in a large number of studies [17]. On the basis of this observation, implantation of implantable cardioverter (ICD) defibrillators is recommended as a class IA indication in primary prevention patients with a LVEF ≤ 30% in NYHA class I and patients with a LVEF ≤ 35% in NYHA class II-III [18]. In our study, univariate analysis shows the importance of reduced LVEF (24.6±4.9%) as a predictor of frequent ICD shocks (P=0.04).

On the other hand, several clinical trials revealed that patients who received appropriate ICD therapy have a higher mortality than patients who do not. The results of MADIT II along with the results of the SCD-HeFT, both appropriate and inappropriate ICD therapy were associated with a higher mortality [19, 20]. T. Marynissen et al. described ICD resistant mortality and concluded that it was four times more likely for patients with a reduced left ventricular function to die despite their ICD [21]. Therefore, the need for other risk predictors to provide clinically useful information about ICD shocks and death with reduced LVEF increased.

Several post-MI studies showed that the presence of NSVT or frequent premature ventricular complexes in Holter recordings were predictive of serious arrhythmic events and death [22]. With this association, MUSTT and MADIT I trials which evaluated the role of an ICD in patients with a prior MI and LV dysfunction, used NSVT as an inclusion criterion [23, 24]. Our results were supporting the findings of these studies.

NSVT was found statistically significant in frequent ICD therapy group (P=0.021). However, MADIT II and SCD-HeFT showed a survival benefit with ICD therapy in patients with reduced LVEF even in the absence of NSVT [25, 26]. Due to limited predictive value of NSVT, additional risk stratifications were investigated to enhance the predictive power in addition to EF measurement.

HRV was accepted as a measure of autonomic regulation of cardiac activity. Reduced HRV which was considered as a marker for autonomic dysregulation reflected both decreased parasympathetic and increased sympathetic activity. ATRAMI was the first large study which showed the prognostic value of low heart rate variability (using SDNN values) after an acute myocardial infarction. SDNN < 70 ms pointed out significant risk of mortality particularly in patients with LVEF < 35% [27, 28]. Nolan et al. reported that reduced HRV was associated with NYHA functional class, left ventricular diastolic dimension, reduced left ventricular ejection fraction, and peak O_2 consumption in patients with heart failure. They concluded that depressed HRV on holter monitoring was an independent risk factor for a poor prognosis in patients with congestive heart failure (CHF) [29, 30]. In our study we could not find any relationship between SDNN and frequent ICD shock therapy (P=0.09). Frequent and more complex VP beats were identified in our analysis. This finding could be the reason not to show any statistically significant correlation between SDNN which required normal-to-normal beat intervals and ICD shock therapy [26].

HRT was described as a marker of the autonomic response to perturbations of arterial blood pressure after single ventricular premature complexes (VPC) and it was believed to reflect increased sympathetic tone and baroreflex sensitivity. The retrospective studies including MPIP, EMIAT, and ATRAMI showed that impaired HRT were the strongest and independent electrocardiographic predictor of cardiac death in postinfarction patients. In these studies patients with both abnormal TO and TS had high mortality risk than just based on low ejection fraction [9, 31]. Barthel et al. documented prognostic value of HRT in patients with acute myocardial infarction (prospective ISAR-HRT study). In this study combination of abnormal HRT parameters and decreased LVEF (< 30%) was found to be an independent predictor of mortality [HR, 4.5] [32].

FINGER study aimed to show predictive power of Holter-based risk variables including NSVT, SDNN, and spectral measures of HR variability, HR turbulence, and fractal HR variability index as predictors of sudden cardiac death among survivors of acute myocardial infarction patients. Reduced post-ectopic turbulence slope (TS) (P < 0.001) and non-sustained ventricular tachycardia (P < 0.01) were found marked SCD predictors after adjustment for age, diabetes, and ejection fraction (EF). In subgroup analysis this predictive accuracy could not be attributed to SCD among patients with reduced LV function (EF < 35%) [15]. The reason why such Holter variables predicted SCD were somewhat disappointing could be explained by altered autonomic regulation of heart rate dynamics and electrical vulnerability of heart failure. Nevertheless, Cygankiewicz et al. pointed out abnormal HRT's significance of all-cause mortality, sudden death and death due to heart failure progression in patients with congestive heart failure including ischemic and nonischemic causes [33]. Miwa et al. also revealed importance of combined assessment of HRT and NSVT to predict SCD and life threatening arrhythmias than other risk variables in patients with LV dysfunction with an HR of 8.2 (95% CI, 2.9-23.3; P < 0.0001) on multivariate analysis [10]. Severe left ventricular dysfunction diminishes vagal activity and influences the HRT parameters [34]. This situation may facilitate ventricular arrhythmias. Iwasa, et al. found abnormal HRT prior to programmed ventricular stimulation predicted the induction of sustained ventricular arrhythmias in patients with ischemic cardiomyopathy. But in ambulatory settings, HRT was detected to predict spontaneous rather than induced ventricular arrhythmias [35]. In agreement to this study, we found strong relationship between abnormal HRT and frequent shocks in patients with ischemic cardiomyopathy. HRT parameters named TS and TO show this link as well. The multivariate analysis of HRT categories and other holter parameters reveal TS and NSVT to be predictive for frequent ICD shock outcome in both groups. These findings could be explained by multiple ICD shocks enhance cellular damage beyond reduce LV function. This observation is reflected by blunted TS, TO and the occurrence of NSVT.

In predicting frequent ICD shocks as a result of serious VTs, assessment of trending holter variables such as TS and NSVT appears to be reliable methodology in patients with ischemic cardiomyopathy (EF < 35%).

Limitations

The main limitations are number of patients enrolled in this study was not large enough and device programming in ICD patients before and after shock therapy were not mentioned. Holter parameters were investigated after patients' experienced ICD shock therapy and received medical treatments. However, we found no significant differences about medical treatments even include beta blocker therapy between groups and these treatments did not appear to effect on the result of holter analysis. Because of limited extent of this study, we also do not know cardiovascular mortality and further arrhythmic events.

Conclusion

In conclusion, frequent ICD shock should prompt physicians to consider noninvasive risk stratifications. Our study reveals that presence of NSVT and abnormal TS can predict frequent ICD shocks in ischemic cardiomyopathy patients. However, further prospective investigations with larger populations are needed to get more accurate results.

Disclosure of conflict of interest

None.

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