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Deceleration capacity: A novel predictor for total mortality in patients with non-ischemic dilated cardiomyopathy

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ABSTRACT

Objectives: We hypothesized that deceleration capacity (DC), a novel marker of cardiac autonomic modulation, is an independent predictor for mortality in patients with non-ischemic dilated cardiomyopathy (NICM).
Background: NICM is associated with a high risk for sudden cardiac death (SCD). However there are no clinically established parameters available for risk stratification beyond LVEF.
DC has been previously shown to be a strong independent predictor for total mortality in patients after myocardial infarction.
Methods: Holter-ECG recordings of 201 patients NICM (83.1% male, mean age: 61.4 years, mean LVEF: 33.3%) were analyzed by the method of phase-rectified-signal-averaging (PRSA) to obtain DC.
Results: During a minimum follow-up of 40 month 59 patients died. Kaplan Meyer Analysis showed a significantly higher mortality in patients with a DC below 4.5 ms (log rank $p = 0.012$) irrespective to the presence of atrial fibrillation.
Conclusions: Impaired DC is a powerful independent predictor for mortality in patients with NICM.

1. Introduction

Implantable cardioverter defibrillator (ICD) therapy is an established therapy in patients with heart failure and significantly reduced left ventricular ejection fraction (LVEF), irrespective to the underlying structural heart disease [1,2]. There are various established parameters available for risk stratification in patients with ischemic heart disease [3–6]. Many of these parameters except LVEF have failed as independent predictors for mortality in patients with non-ischemic dilated cardiomyopathy (NICM) [7]. However in patients with NICM reduced LVEF did not show efficacy as exclusive inclusion criteria for ICD-therapy presumably because of a markedly higher number needed to treat [8–11]. Despite this fact, risk stratification in patients with NICM in the present routine primarily relies on clinical symptoms and imaging techniques such as echocardiography, cardiac magnetic resonance and angiography to evaluate LVEF [2]. Therefore it is eminent to find parameters beyond LVEF that independently predict overall mortality and risk for SCD in this patient cohort.

Deceleration capacity a novel Holter-Electrocardiogram (ECG) derived marker of heart rate variability (HRV) has recently proven to be a strong predictor of mortality independent of LVEF in patients surviving acute phase of myocardial infarction [12,13].

This innovative parameter has not been investigated concerning its prognostic relevance in patients with NICM. In a small pilot-study reduction of DC could be demonstrated in patients with NICM with and without SCD [14].

Therefore we postulated that DC could be an independent predictor of mortality in patients with NICM.

2. Methods

A total number of 325 consecutive patients admitted to the hospital with the diagnosis NICM were prescreened for this study. NICM was diagnosed by significantly reduced LVEF in the absence of flow-limiting coronary artery disease [15]. Patients without valid Holter-ECG-recordings (recording time below 20 h, excessive noise), without evaluation of LVEF within the past year, without invasive exclusion of coronary artery disease and with severe malignant diseases and suspected death within the following 3 month were not held applicable for the study and therefore not included. A total number of 201 patients where included into the study. Overall mortality was accessed by registry office information.

In order to calculate DC the method of phase-rectified signal averaging (PRSA) [16] was used to process sequences of RR intervals from the selected recording periods. PRSA extracts periodicities from complex time series. In a first step all Holter-ECG-Recordings

Abbreviations: ICD, Internal cardioverter defibrillator; LVEF, Left ventricular ejection fraction; ECG, Electrocardiogram; HRV, Heart rate variability; DC, Deceleration capacity; NICM, Non ischemic dilated cardiomyopathy; PRSA, Phase rectified signal averaging; NYHA, New York Heart Association classification of Heart failure; AF, Atrial fibrillation; SDNN, Standard deviation of normal to normal intervals; SDANN, Standard deviation of averaged normal to normal intervals; rMSSD, Square root of the mean of the sum of squared differences between adjacent normal- to-normal intervals; HF, High frequency domain in power spectral density analysis; LF, Low frequency domain in power spectral density analysis; HFpEF, Heart failure with preserved ejection fraction (≥35%).

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are manually checked for classification of normal beats and premature beats as well as artifacts that are deleted from the recording. To suppress errors due to artifacts, RR interval prolongations of more than 5% are excluded. For computation of DC anchors are put into a tachygram, which presents a plot of all RR intervals recorded. An anchor point is defined as RR0. The two preceding RR-intervals, defined as RR-1 and RR-2, as well as the RR-interval following RR0 (RR + 1) built four-beat-segments which are used in the analysis. These four beat segments are averaged, after all RR-prolongations >5% are excluded from the analysis. The mean values of RR-2, RR-1, RR0 and RR + 1 are used in the equation $DC = [X(0) + X(1) - X(-1) - X(-2)] / 4$ to calculate DC. A distinct introduction of the measurement and computing has been published before [12,13,16].

2.1. C. Statistical analysis

Continuous variables where tested for normal distribution using Kolmogorov–Smirnov goodness-of-fit test. Statistical significance was estimated using Students-*T*-Test if two conditions were compared and one-way ANOVA if more than two conditions were compared. For statistical analyses all parameters are given as mean ± standard deviation (SD). Survival analysis was performed using Kaplan Meyer Survival Analysis (KMSA) with log-rank-analysis to reveal level of significance. A p-value of less than .05 was considered statistically significant. Statistical analysis was performed using SPSS 15.0 (Chicago, Illinois, USA) and Microsoft Excel (Microsoft Inc., California, USA). Graphics were plotted with MedCalc (MedCalc Software bvba, Ostend, Belgium) after double-check of statistical measures using SPSS.

3. Results

3.1. Patient cohort

The mean follow up period was 54 ± 27 month. Of the 201 investigated patients 167 (83.1%) where male. The mean patient age was 61.4 ± 13.3 years. The mean NYHA-class at admission was 2.5 ± .99 with a high fraction of functional class III and IV (50% of the patients). The mean left ventricular ejection fraction was 33.3 ± 12.3%. Table 1 gives a summary about patient criteria at time of inclusion. Atrial fibrillation (AF) was present in 67 patients (33.3%). Patients with AF were considered separately. During the surveillance time a total of 51 patients died from any cause. A differentiation of cause of death was impossible due to study design.

3.2. Deceleration capacity

Deceleration capacity was significantly higher in surviving patients (5.27 ± 2.79 ms vs. 4.33 ± 2.35 ms; p = .02). The level of statistical significance was consistent after excluding 62 patients with AF (4.71 ± 2.31 vs. 3.5 ± 2.32, p = .018). Fig. 1 shows DC of survivors and non-survivors in all 201 patients and 139 patients without AF. Exclusive analysis of the 130 patients without severely impaired LVEF (≥30%) revealed a significantly higher DC in surviving patients. After excluding patients with atrial fibrillation the level of significance was raised (5.28 ± 2.19 ms vs. 3.30 ± 1.76 ms; p = .001).

For Kaplan Meyer Survival Analysis (KMSA) the patient collectives were divided into two groups by median. The median was 4.5 ms. Area under the curve analysis revealed a cut point close to the median.

Patients with a deceleration capacity ≥4.5 ms had a significantly higher survival rate than patients with a DC < 4.5 ms. Analysis of the entire patient collective showed a p-value of log-rank-analysis of .012. This could be comprehended in all patient sub-collectives. The level of significance was raised after excluding patients with AF (p = .003). There were also significant differences between the groups in separate analysis of patients with an LVEF ≥30% (p = .021) but not within the group of patients with highly impaired LVEF <30%. After exclusion of patients with AF within the group of patients with LVEF ≥30% the level of significance was raised (p < .001). The results were likewise if the cutoff point for LVEF was 35%. An overview is shown in Table 2. KMSA of DC in different patient collectives is presented in Fig. 2.

In a discrete analysis of the 143 patients without previous implantation of an internal cardioverter defibrillator KMSA also revealed a significant difference between the two groups , with DC above and below 4.5 ms (p = .026).

Evaluation of DC in relation to NYHA functional class revealed no significant differences in ANOVA-testing between groups.

3.3. Relation of DC to classical parameters of HRV

Deceleration capacity showed a high level of correlation to classical parameters of HRV such as mean heart rate (HR), as well as parameters of time domain analysis, such as SDNN and parameters of frequency domain such as HF and LF. See Table 3 for an overview of correlation coefficients. Survival analysis applying these parameters did not show significant findings in the general population and after excluding patients with atrial fibrillation.

Table 1
Clinical parameters of the patient collective. Clinical characteristics of the general study population and after excluding patients with atrial fibrillation in Holter-ECG. NYHA = New York Heart Association, MAP = mean arterial pressure, LBBB = Left bundle branch block, ACE = angiotensin converting enzyme, AT1 = angiontensinogen 1, and ICD = internal cardioverter defibrillator.

Clinical parameters	All patients n = 201	Patients w/o AF n = 139	Patients with AF n = 62	p-Value
Age (years)	61.4 ± 13.3	59.7 ± 9.7	65.6 ± 10.0	.005
Male sex, n (%)	167 (83.1)	114 (82)	53 (85)	n.s.
NYHA functional class, n (%)				.007
I	42 (20)	35 (25.2)	22 (35.4)	
II	57 (28.9)	35 (25.2)	29 (46.8)	
III	68 (33.8)	39 (28.1)	3 (4.8)	
IV	34 (17.3)	19 (19.4)	7 (11.3)	
Left ventricular ejection fraction, n (%)	33.3 ± 12.3	32.7 ± 12.8	34.8 ± 10.9	n.s.
Systolic blood pressure (mm Hg)	127.0 ± 18.7	124.8 ± 15.5	131.5 ± 20.5	.02
Diastolic blood pressure (mm Hg)	76.0 ± 12.3	74.3 ± 12.1	79.8 ± 12.1	0.03
Sodium serum level (mmol/l)	138.3 ± 4	138.4 ± 3.9	138.1 ± 4.3	n.s.
Potassium serum level (mmol/l)	4.04 ± .47	4.06 ± .48	3.98 ± .44	n.s.
Creatinine serum level (μmol/l)	94.1 ± 30.9	91.3 ± 24.9	100.3 ± 40.9	n.s.
Heart rate (beats per minute)	84.9 ± 25.3	81.8 ± 24.7	91.7 ± 25.3	.01
QRS duration (ms)	109 ± 30 ms	113 ± 31	101 ± 26	.01
LBBB, n (%)	59 (29.4)	47 (33.8)	12 (19.4)	.05
ACE-inhibitor or AT1-antagonist at discharge, n (%)	187 (94.7)	128 (92.1)	59 (95.2)	n.s.
β1-Receptor-blocker at discharge, n (%)	189 (94)	131 (94.2)	58 (93.5)	n.s.
Loop-diuretic at discharge, n (%)	156 (77.3)	104 (74.8)	52 (83.9)	n.s.
Aldosteronantagonist at discharge, n (%)	110 (54)	72 (52.6)	38 (61.3)	n.s.
Amiodarone at discharge, n (%)	31 (14.3)	20 (14.4)	9 (14.5)	n.s.
Digitalis at discharge, n (%)	66 (32.8)	32 (23)	34 (54.8)	.0005
ICD at discharge, n (%)	58 (28.9)	52 (37.4)	6 (9.7)	.0005