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ORIGINAL ARTICLE

Decreased Deceleration Capacity of Heart Rate Detects Heart Failure Patients at Risk for Malignant Ventricular Arrhythmias

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KEY WORDS: *deceleration capacity of heart rate; autonomic nervous system; arrhythmic sudden cardiac death; risk stratification; heart failure; ventricular tachyarrhythmias; implantable cardioverter defibrillator*

ABBREVIATIONS
AC = acceleration capacity (of heart rate)
ANS = autonomic nervous system
CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
DC = deceleration capacity (of heart rate)
DCM = dilated cardiomyopathy
EPS = electrophysiology study
fQRS = filtered QRS
HRT = heart rate turbulence
HRV = heart rate variability
ICD = implantable cardioverter defibrillator
LAS = low amplitude signal
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NSVT = non sustained ventricular tachycardia
QTc = rate corrected QT interval
RMS = root mean square
SAECG = signal averaged electrocardiogram
SCD = sudden cardiac death
VF = ventricular fibrillation
VPBs = ventricular premature beats
VT = ventricular tachycardia

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ABSTRACT

BACKGROUND: Deceleration capacity (DC) of the heart rate has proved an independent predictor of total mortality in post-myocardial infarction (post-MI) patients but it is unknown whether DC predicts the arrhythmic risk as well.

OBJECTIVE: Our aim was to investigate whether DC can predict the arrhythmic sudden cardiac death (SCD) surrogate in patients with heart failure (HF).

PATIENTS AND METHODS: We prospectively screened 145 HF patients with electrocardiogram (ECG), signal averaged ECG, echocardiography, and 24-hour Holter ECG. After 41.2 months, patients were divided into high (n=43) and low risk (n=102) groups according to three arrhythmic surrogates: clinical ventricular tachyarrhythmia (ventricular tachycardia -VT/ ventricular fibrillation-VF) (n=18), appropriate activation of the implantable cardioverter defibrillator (ICD) device (n=23) and confirmed SCD (n=2).

RESULTS: High risk patients had impaired DC with significantly lower values (3.2±1.8 ms vs 4.0±2.1 ms, p=0.025). In the Cox regression analysis model adjusted for age, gender, diabetes, left ventricular ejection fraction (LVEF), filtered QRS, QTc, non-sustained VT episode(s) ≥1/24 h, ventricular premature beats ≥240/24 and DC, DC emerged as an important SCD surrogate predictor with a hazard ratio of 0.804, (95% confidence intervals-CI: 0.671- 0.963, p = 0.018). The cutoff point of DC ≤3.352 ms (median) presented a hazard ratio of 2.885 (95% CI: 1.342 - 6.199, p=0.007, log rank test: p=0.003) for SCD surrogate.

CONCLUSION: Decreased DC was found to be an important and independent SCD surrogate predictor. The cutoff point of DC ≤3.352 ms detects HF patients at increased arrhythmic risk.

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INTRODUCTION

Heart failure (HF) patients face an increased risk for arrhythmic sudden cardiac death (SCD).[1] Malignant ventricular arrhythmias constituted a serious lethal threat in the period before 1980, when the implantable cardioverter defibrillator (ICD) was introduced as the definite prophylactic therapy by Dr Mirowski.[2] After the establishment of the ICD as an efficient therapeutic technique for the protection of patients against fatal ventricular arrhythmias,[3] a new clinical challenge emerged, i.e. although the final prophylactic therapy was known, the patient being a candidate for this lethal arrhythmic risk was not well defined. In order to solve this problem, different risk stratification strategies were introduced and applied.[4]

Nowadays, the left ventricular ejection fraction (LVEF) is used as the prevailing conventional arrhythmia risk stratifier even though it is associated with low sensitivity. Current research is focused on the development of new risk stratification methods. Among the predictors for adverse outcomes in post-myocardial infarction (MI) patients, the deceleration capacity (DC) of the heart rate has been recently proposed.[5] Previous studies demonstrated DC's impairment in post-MI patients at an increased risk for death,[6] in schizophrenics on antipsychotic drugs,[7] in post-MI patients prior to nonsustained ventricular tachycardia (VT) episodes,[8] while in combination with an impaired heart rate turbulence (HRT), reflecting severe autonomic failure, it was associated with an adverse outcome in post-MI patients even with a preserved LVEF.[9]

As it is not clear whether DC, apart from total mortality, has any prognostic ability for predicting the arrhythmic SCD of HF patients' risk as well, we designed the present study in an attempt to provide some answers.

METHODS
PATIENTS AND STUDY DESIGN

This prospective observational study was approved by our Institution's Ethics Committee and all participants provided their informed consent. Subjects were hospitalized in our department and were referred to our electrophysiology laboratory for evaluation for primary or secondary prevention of arrhythmic SCD. The study patients had an impaired left ventricular systolic function with a LVEF ≤50% due to coronary artery disease (CAD) or dilated cardiomyopathy (DCM). Exclusion criteria included ongoing myocardial ischemia anticipated to be improved with revascularization, malignant diseases affecting survival such as cancer or leukemia, hepatic cirrhosis, chronic kidney failure on hemodialysis, stroke-mediated hemiplegia, paraplegia, tetraplegia, psychiatric disease, addiction to alcohol/ opioid/ psychiatric medications, dementia and diseases affecting the autonomic nervous system (ANS) causing dysautonomia. Patients with chronic atrial fibrillation were excluded from the study, while those with a history of paroxysmal atrial fibrillation were included provided they were in sinus rhythm during the recruitment phase.

After obtaining a detailed patient personal and family history with medications recording, patients underwent physical examination, chest x-ray, blood and biochemical tests, 12-lead-ECG, echocardiography (Echo), signal averaged ECG (SAECG) and 24-hour ambulatory ECG. Subjects with either nonsustained ventricular tachycardia (NSVT) episodes and/or late potentials were further risk-stratified by electrophysiology study (EPS). Patients with inducible ventricular tachycardia/ ventricular fibrillation (VT/VF) on EPS (n=32) as well as those with clinical VT/VF (n=13/2 overlap) were candidates for an ICD (n=43). From the total sample (n=162), we excluded patients with negative DC values (n=17). We previously proposed[10] that the original DC calculation method[5] may produce negative DC values representing acceleration and not deceleration, a condition contradicting the principle of inter-beat deceleration. In brief, the original DC method uses the following steps[5]: First, all RR intervals longer than the previous RR intervals are characterized as DC anchors. In this way, the method focuses on the inter-beat decelerations. In the next step, segments of the same size of RR intervals around the anchors are selected and consequently aligned to the anchors. The final phase rectified averaged signal is obtained by averaging the signals within the aligned segments. The quantification of DC is based on the following formula: $DC = [X(0)+X(1)–X(–1)–X(–2)]/4$, where X(0) is the average of the RR intervals at all anchors, X(1) and X(–1) are the averages of the RR intervals immediately before and after the anchors and X(-2) is the average of the RR intervals before X(-1).

When we applied the original method on our data,[11] a paradox was observed; some patients produced negative DC values. From the physiology point of view, when the next RR interval decelerates, this cardiac cycle's interval is longer compared to the previous cardiac cycle's duration. In this way, their difference is always positive. A method quantifying and extracting the signal's deceleration capacity is expected to always produce positive values. By examining the original formula, as the algebraic sum is calculated on four averaged intervals, it is possible to extract a negative final algebraic sum in cases where X(-2) and (X-1) intervals are longer compared to X(0) and X(1) intervals. The physiological meaning of a negative value describing inter-beat durations is acceleration and not deceleration. For a deeper understanding, let us consider a model of two (averaged) RR intervals. If the second (averaged) cardiac cycle is longer than the previous one (real deceleration) then only positive DC values must be produced from the difference between these two cardiac cycles. The original method calculates the DC values from a formula using four instead of two (averaged intervals). Because of

the selection of a quad final window for the DC calculation, it is possible in some patients a negative algebraic sum to be extracted. The results of the present study were based on an old analysis made via the original DC method. We decided to exclude those patients with negative DC values given the computed DC value was not reflecting the real deceleration of heart rate.

The mean LVEF of the included patients was depressed (LVEF = 32.3±10.1%). The follow-up period was 41.2 months. The primary end-point was based on three SCD-surrogate events: 1. Clinical VT/VF (n=18), 2. SCD (n=2), 3. ICD appropriate activation (n=23). The secondary end point was total mortality (n= 38). Follow up was completed with annual reexamination in the outpatient clinic and with telephonic contact. Study's end-points were double checked with the ICD's interrogation reports provided from the physicians implanting the devices.

ECG AND SIGNAL AVERAGED ECG (SAECG)

Each participant while in sinus rhythm underwent a resting supine ECG at 25 mm/sec and a SAECG (MAC 5000 GE Medical, Milwaukee, USA) in the same position by the use of the three X, Y, Z orthogonal bipolar leads (filter: 40-250 Hz). Conventional criteria for the presence of late potentials were used (fQRS: ≥114 ms, LAS: ≥38 ms, RMS: ≤20 μV) for those with normal QRS,[12] but for patients with intraventricular conduction delay with QRS duration ≥120 ms, the modified criteria were applied (fQRS: ≥145 ms, LAS: ≥50 ms, RMS: ≤17.5 μV).[13]

ECHOCARDIOGRAPHY

A complete echocardiographic examination was performed (SONOS 5500, Hewlett Packard, Andover, Massachusetts, USA). LVEF was calculated according to the recommendations of the American Society of Echocardiography.[14]

24-HOUR HOLTER MONITORING (HM)

During the hospitalization period, every patient in sinus rhythm underwent 24-hour Holter monitoring (HM) (Spider View-1000Hz). The recordings were analyzed using SyneScope 3.10 software (Spider View & Synescope 3.10, Sorin Group, Clamart, France). The events were reviewed and manually corrected by a dedicated researcher. The following were calculated: heart rate, RR intervals, ventricular premature beats (VPBs), and NSVT episodes. For heart rate variability indices (HRV), the included patients had at least 18 hours of good quality signal recordings, including less than 12% of filtered extra systoles. HRV analysis guidelines were fully observed.[15]

Heart Rate Variability Time Domain Analysis: The standard deviation (SD) of the normal to normal RR intervals (SDNN) was automatically calculated by Synescope 3.10 software.

Rate Corrected QT Interval: For Holter derived QTc interval, a mean complex waveform was calculated based on 30 seconds of ECG by the SyneScope 3.10 software. The mean 24-hour value of QTc calculated values was extracted as a QTc index. Fredericia's formula was applied for the rate correction.[16]

Deceleration Capacity (DC): For the computation of DC and AC the mathematical method based on the original algorithm provided for research purposes from the Working Group of Biological Signal Analyses in Technische Universität München[17] was applied on extracted RR time series from the patient's 24 hour Holter recordings.

ELECTROPHYSIOLOGY STUDY (EPS)

A complete electrophysiology study (EPS)[18] was performed on informed consented patients with either NSVT episodes or late potentials (n=58). Ventricular tachycardia inducibility during EPS was defined as induction of either sustained monomorphic VT and/or polymorphic VT degenerating into VF (n=32).

STATISTICAL ANALYSIS

Continuous variables are presented as mean values ± SD (standard deviation), while qualitative variables are shown as relative frequencies. Differences in clinical characteristics between the two groups were investigated with t- and Chi-square tests. For the purpose of univariate analysis, t-test and log rank were applied to examine the associations between non-invasive markers and SCD surrogate end points. Multivariate analysis was performed using Cox regression models adjusted for age, gender, diabetes, LVEF, fQRS, QTc (Fredericia), NSVT >1/24h, VPBs>240/24h and DC (continuous/dichotomous values). A backward elimination process was applied on all multivariate models (using p <5% as the threshold for removing a variable from the models). All reported p-values are based on two-sided tests and compared to a significance level of 5%. The results obtained are presented as hazards ratios (HR) and the 95% confidence intervals (C.I.). The STATA 8.0 software (Stata Corporation 2003, Texas, USA) was used in all statistical calculations. A value of p <0.05 was considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS

Patients' mean age was 64.5±12.3 years; 83% were males. Mean LVEF was 32.3±10.1%. Coronary artery disease (CAD) was present in 82% of the patients and dilated cardiomyopathy (DCM) in 18%. Mean follow-up period was 41.2 months. No differences between SCD+ and SCD- surrogate patients were observed in age, gender, CAD, ST-elevation MI (STEMI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), DCM, diabetes mellitus, hematocrit, renal

function, sodium, potassium and medications. In contrast, the SCD+ surrogate group was different in comparison to the SCD- surrogate group in LVEF (28.0±9.2% vs 34.1±9.9%, p<0.001) and New York Hear Association (NYHA) class (2.5±0.5 vs. 2.2±0.5, p=0.002). EPS was performed on 58 patients with 32 patients demonstrating inducible VT/VF (55%). Baseline clinical characteristics are presented in Table 1.

UNIVARIATE ANALYSIS

When our data were analyzed for the SCD surrogate primary end point, the univariate analysis revealed a significant difference between the SCD+ and SCD- surrogate groups for LVEF (28.0±9.2% vs 34.1±9.9%, p<0.001), for LV end-diastolic diameter (LVEDD) (60.2±8.1 mm vs 56.3±8.9 mm, p=0.026) and for fQRS from SAECG late potentials analysis (144±29 ms vs 133±28 ms, p=0.054) while the VPBs cutoff point ≥240 episodes/24h (55% vs 37%, p=0.039) and SDNN (80±29ms vs 96±36 ms, p=0.009) were also found statistically different for the two groups. DC was found essentially decreased in SCD+ surrogate patients (3.2±1.8 ms vs 4.0±2.1 ms, p=0.025), whereas AC was not found statistically different between the two groups. The results of the univariate analysis for arrhythmic end points are presented in Table 2. It is known that DC predicts all-cause mortality. Our results for the total mortality end point are in accordance with the results of previous studies confirming them.[5] In the univariate analysis, DC was substantially lower in the deceased group (2.8±1.6 ms vs 4.1±2.1 ms, p<0.001), while the LVEF was also found signifi-

TABLE 1. Baseline Patient Characteristics

Characteristics	Total (n=145)	SCD + (n=43)	SCD - (n=102)	p value
Age (years)	64.5±12.3	66.2±11.8	65.1±12.5	0.627
Male sex (%)	83	84	81	0.114
CAD (%)	82	86	80	0.418
STEMI (%)	55	53	56	0.772
Non STEMI (%)	10	19	6	0.018
CABG (%)	33	35	32	0.668
PCI (%)	27	16	32	0.090
DCM (%)	18	14	20	0.537
Diabetes (%)	33	36	32	0.617
LVEF (%)	32.3±10.1	28.0±9.2	34.1±9.9	<0.001
NYHA class	2.2±0.5	2.5±0.5	2.2±0.5	0.002
Ht (%)	41±5	40±5	41 ±5	0.251
Urea (mg/dl)	53±30	59±38	50±26	0.175
Creatinine (mg/dl)	1.3±0.5	1.3±0.4	1.3±0.6	0.995
Sodium (meq/L)	138±3.4	138±3.4	138±3.5	0.922
Potassium (meq/L)	4.3±0.5	4.2±0.5	4.3±0.5	0.401
Medications				
Beta-blockers (%)	64	57	67	0.262
Diuretics (%)	58	62	56	0.527
Amiodarone (%)	19	25	17	0.296
CCBs (%)	12	17	10	0.298

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCBs = calcium channel blockers; DCM = dilated cardiomyopathy; Ht = hematocrit; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association (class); PCI = (primary) percutaneous coronary intervention; Non STEMI = non-ST elevation myocardial infarction; SCD = sudden cardiac death (surrogate); STEMI = ST-elevation myocardial infarction

TABLE 2. Arrhythmia Predictors (Mean Values) for SCD+ Surrogate and SCD- Surrogate Groups

Predictors	All (n=145)	SCD+ (n=43)	SCD - (n=102)	p value
ECHO				
LVEF (%)	32.3±10.1	28.0±9.2	34.1±9.9	<0.001
LVEDD (mm)	57.4±8.8	60.2±8.1	56.3±8.9	0.026
SAECG				
fQRS (ms)	136±29	144±29	133±28	0.054
LAS (ms)	47±29	54±30	44±28	0.065
RMS (μV)	26±17	22±17	28±17	0.082
Noise level(μV)	0.34±0.14	0.37±0.21	0.33±0.10	0.114
HOLTER				
NSVT>1/24h (%)	27	37	23	0.099
VPBs>240/24h (%)	42	55	37	0.039
HR24h(bpm)	70±10	71±11	69±9	0.207
SDNN 24h(ms)	91±35	80±29	96±36	0.009
QTc (ms)Fredericia	435±32	440±38	432±29	0.181
DC	3.8±2.1	3.2±1.8	4.0±2.1	0.025
AC	-5.8±2.5	-5.4±2.7	-6.0±2.4	0.255

AC = acceleration capacity (of heart rate); DC = deceleration capacity (of heart rate); ECHO = echocardiography; HR = heart rate; fQRS = filtered QRS; LAS = low amplitude signal, LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; NSVT = non sustained ventricular tachycardia; QTc = (rate) corrected QT interval; RMS = root mean square; SAECG = signal averaged electrocardiogram; SDNN = standard deviation normal to normal beat from heart rate variability analysis; SCD = sudden cardiac death; VPBs = ventricular premature beats.

cantly reduced in the patients who had deceased (29.2±9.8% vs 33.4±10.0%, p=0.025).

MULTIVARIABLE ANALYSIS

Multivariate analysis for the arrhythmic SCD surrogate end point was performed with Cox regression analysis. The basic model was adjusted for gender, age, diabetes, LVEF, fQRS, NSVT ≥1episode/24h, VPBs ≥240beats/24h, QTc (Fredericia), and one variable from the 2 indices assessing the ANS activity (DC continuous, dichotomous cutoff of DC ≤3.352 ms) was added to it each time. Important and independent predictors for arrhythmic SCD surrogates proved to be the LVEF with a hazard ratio of 0.944 (95% C.I.: 0.908-0.981, p=0.004), the DC continuous with a hazard ratio of 0.804 (95% C.I.:0.671-0.963, p=0.018), while the dichotomous cutoff point of DC ≤3.352 ms (median) presented a hazard ratio of 2.885 (95% CI: 1.342 – 6.199, p=0.007) for arrhythmic SCD surrogates (Log rank test, p=0.003). The Kaplan Meier curves for the arrhythmic end point (SCD surrogate) are presented in Figure 1. Results of the multivariate analysis for SCD end point are presented in Table 3. Multivariate analysis for the total mortality was

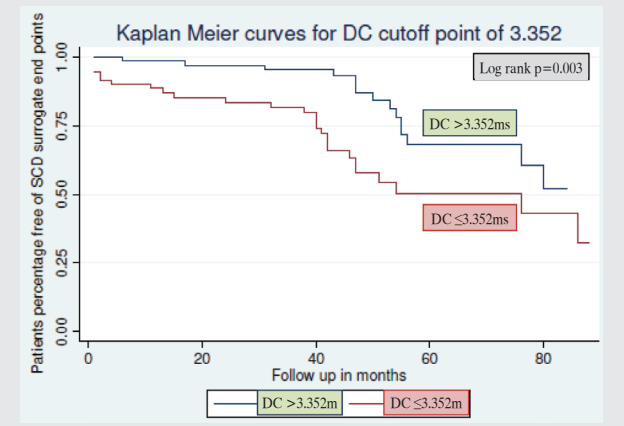

FIGURE 1. Kaplan Meier curves for arrhythmic end points. The subgroup of patients with decreased deceleration capacity (DC), under the dichotomous value of DC ≤3.352 ms, present high frequency of arrhythmic events, while the patients with preserved deceleration capacity, above the DC >3.352 ms cut off point, present lower rates of arrhythmic events. This difference is significant: Log rank test = 0.003. SCD = sudden cardiac death.

TABLE 3. Multivariate Cox Regression Analysis of the Predictors for the Occurrence of SCD Surrogate

Variables	Hazard Ratio	(95% CI)	p value
Male	0.397	0.154-1.027	0.057
Age	0.975	0.947-1.003	0.088
LVEF	0.944	0.908-0.981	0.004
fQRS	-	-	NS
NSVT>1/24h	-	-	NS
VPBs>240/24h	-	-	NS
QTc	-	-	NS
DC	0.804	0.671-0.963	0.018
AC	1.154	0.999-1.335	0.052
DC Cut off 3.352 ms	2.885	1.342-6.199	0.007

Basic model adjusted for: Gender, Age, Diabetes, LVEF, fQRS, NSVT >1/24h, VPBs >240/24h, QTc and one of the variables of DC (DC continuous /DC cut off point 3.352 ms) applied on the basic model each time. Log rank for DC ≤3.352 ms, p = 0.003.
AC = acceleration capacity of heart rate; CI = confidence intervals; DC = deceleration capacity of heart rate; LVEF = left ventricular ejection fraction; fQRS = filtered QRS from signal averaged ECG; NS = not (statistically) significant; NSVT = non sustained ventricular tachycardia (episodes); QTc = rate corrected (according with the Fredericia formula) QT interval derived from Holter recordings; SCD = sudden cardiac death; VPBs = ventricular premature beats

also performed with Cox regression, the model being adjusted for gender, age, diabetes, LVEF, fQRS, NSVT ≥1/24h, VPBs ≥240/24h, QTc and DC continuous. In this model, the DC continuous showed a hazard ratio of 0.727 for total mortality (95% C.I.: 0.580 - 0.911, p value=0.006). When the cutoff point of DC 3.352 ms (median) was added to the same Cox regression model replacing the DC continuous, a hazard ratio of 2.545 for total mortality was revealed for the patients subgroup with DC values below this cutoff point (95% C.I.: 1.103-5.870, p value =0.028 and Log rank test: p=0.011).

DISCUSSION

For the first time, we investigated how the deceleration capacity (DC) method performs when used in arrhythmic SCD surrogate risk prediction by analyzing data in an HF patient cohort manifesting systolic ventricular dysfunction. We also described that the DC original method, by using a final quad window of averaged RR intervals, may produce negative DC values. After exclusion of these negative DC values, we found that a DC dichotomous cutoff point of 3.352 ms presents a hazard ratio of 2.885 for arrhythmic SCD surrogate and a hazard ratio of 2.545 for total mortality. These results support the hypothesis that DC may predict both the SCD surrogate and total mortality among HF patients with depressed LVEF, thus emerging as a promising new tool for the arrhythmic risk stratification. Our multivariate Cox regression model was adjusted for several well-established arrhythmic predictors related to different arrhythmia mechanisms (myocardial substrate and scar, repolarization prolongation, extrasystolic triggering, trend for ventricular tachyarrhythmia initiation). The results of the present study support the conclusion that DC is an important and independent risk predictor for major arrhythmic events among post-MI and DCM patients with significant systolic left ventricular dysfunction. In our study, the mean DC of the SCD+ surrogate group patients was 3.2±1.8 ms and their mean LVEF was 28.0±9.2%. Our DC results extracted from patients with severely depressed left ventricular systolic function are similar to the ones reported in the first clinical DC study.[5] It seems that the more the DC value decreases, the more both the risk for total mortality and the risk for SCD increase. In terms of physiology, it has been conceived that DC, by quantifying the inter-beat decelerations, reflects the fast parasympathetic activity regulating the heart rate at the sinus node level.[5] Considering the phase rectification averaged signal technique properties,[19] it has also been assumed that DC expresses the overall deceleration capacity of the sinus node without being linked necessarily to one particular physiological process.[5] It is rational to suppose that DC is mainly related to the parasympathetically mediated autonomic regulation of the heart rate, a function characterized as cardioprotective.[20]

It is known that the parasympathetic activity is decreased in the HF syndrome and the degree of this impairment is correlated with the severity of left ventricular systolic dysfunction.[21] Vagus nerve activity presents cardioprotective and antiarrhythmic properties[20] in animal models with experimentally induced ischemia. It has been shown that vagal stimulation has a beneficial effect on VF thresholds[22] and on ventricular refractoriness.[23] Long lasting observations featured parasympathetic stimulation as a new possible therapeutic target in HF patients.[24]

In conditions where this autonomic regulation is impaired, alike those met in some of our post-MI and DCM patients in the present study, ventricular tachyarrhythmias may be facilitated.[20] Indeed, apart from the underlying arrhythmia substrate of these patients with the myocardial scar, the slow conduction zones and the complex ventricular ectopy, an additional catecholamine mediated triggering mechanism or the absence of adequate cholinergically mediated protective mechanism may facilitate the development of malignant ventricular arrhythmias related to the coexistence of autonomic dysfunction.

In our opinion, it is early to answer whether DC is a specific arrhythmic predictor or a general risk factor for all-cause mortality, given the lack of a prospective large study including a sufficient number of arrhythmic end points. To provide a definite answer, further studies analyzing both end points are required. Such studies are currently ongoing and their results are anticipated with interest.[25-27] The physiological origin, the properties and the range of normal values in healthy persons for DC are issues for investigation.

FUTURE IMPLICATIONS

The DC method seems complicated but as a matter of fact it is not; it is reliable and closely related to the physiology of the heart rate. The introducing researchers, proposed a fully automated technique limiting the inter- and intra-observer variability. They also employed filters to make the analysis even more robust. The algorithm can be clinically widely applied and it has already been incorporated into modern commercially available Holter recorders. Apart from its application in the risk stratification process of post-MI and DCM patients, it could further be used in combination with the heart rate turbulence method for the detection of autonomic failure in several other diseases. The DC method is currently used in research.[25-27] Hopefully, it could build up additional data to the autonomic nervous system assessment beyond the ones investigated by the conventional indices of the heart rate variability.

The research group that introduced the DC method established cutoff points predicting the intermediate and high risk patients for total mortality.[5] Whether these cutoff points are affected by the negative values produced by the original method[5] and whether these cut off points can also predict the SCD risk or new dichotomous values need to be applied on different patient populations are issues requiring further investigation. Our research team developed two new methods, the DC sign of fraction that uses new filtering and the beat to beat DC that calculates DC from a window of two averaged beats.[10] Both these two new DC methods were clinically applied and preliminary results are encouraging.[28]

LIMITATIONS OF THE STUDY

A major limitation of the study was its small patient sample size. The total sample included only 145 patients with 43 SCD surrogate end points. SCD is a very important issue and any conclusion referring to its prediction must be extracted and proposed with caution. Although we trust our data, we would welcome the results of larger prospective studies evaluating the DC performance for SCD prediction and duplicating our preliminary pilot study results. The SCD surrogate end point used in our study included major arrhythmia events occurring either clinically and spontaneously terminated or interrupted by an ICD. Whether these events reliably reflect the SCD risk has been recently questioned.[29] Furthermore, the relatively small number of SCD end points, limits the multivariate analysis as the models may be adjusted only for a small number of variables.

CONCLUSION

Decelerated capacity (DC) predicts total mortality in post-MI and DCM HF patients. The present study provides preliminary evidence that DC may also predict the arrhythmic SCD risk among these patients as well. The originally proposed DC algorithm may in some cases produce negative values. Such results reflect acceleration of the heart rate rather than deceleration and were excluded from our analysis. The DC method is reliable, closely related to the physiology of the heart rate and the DC index is easy to be calculated via commercially available Holter software. In the near future, the method is expected to be increasingly applied in the daily clinical practice as it will constitute a valuable tool in the risk stratification process of post-MI and DCM patients.

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REFERENCES

1. Gatzoulis K, Archontakis S, Dilaveris P, et al. Ventricular arrhythmias: from the electrophysiology laboratory to clinical practice. Part II: Potentially malignant and benign ventricular arrhythmias. *Hellenic J Cardiol* 2012;53:217-233.
2. Mirowski M, Mower MM, Langer A, Heilman MS, Schreibman J. A chronically implanted system for automatic defibrillation in active conscious dogs. Experimental model for treatment of sudden death from ventricular fibrillation. *Circulation* 1978;58:90-94.
3. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.
4. Arsenos P, Gatzoulis K, Dilaveris P, et al. Arrhythmic sudden

cardiac death: substrate, mechanisms and current risk stratification strategies for the post-myocardial infarction patient. *Hellenic J Cardiol* 2013;54:301-315.
5. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet* 2006;367:1674-1681.
6. Bauer A, Bathel P, Müller A, et al. Risk prediction by heart rate turbulence and deceleration capacity in postinfarction patients with preserved left ventricular function retrospective analysis of 4 independent trials. *J Electrocardiol* 2009;42:597-601.
7. Birkhofer A, Geissendoerfer J, Alger P, et al. The deceleration capacity–a new measure of heart rate variability evaluated in patients with schizophrenia and antipsychotic treatment. *Eur Psychiatry* 2013;28:81-86.
8. Arsenos P, Manis G, Nikolopoulos S, Gatzoulis K, Dilaveris P, Stefanadis C. Deceleration capacity alterations before non-sustained ventricular tachycardia episodes in post myocardial infarction patients. *Computing in Cardiology* 2013;40:145-147.
9. Bauer A, Barthel P, Schneider R, et al. Improved stratification of autonomic regulation for risk prediction in postinfarction patients with preserved left ventricular function (ISAR-Risk). *Eur Heart J* 2009;30:576-583.
10. Arsenos P, Manis G. Deceleration capacity of heart rate: two new methods of computation. *Biomed Signal Process Control* 2014;14:158-163.
11. Arsenos P, Gatzoulis K, Manis G, et al. Reduced deceleration capacity of heart rate risk stratifies patients presenting with preserved left ventricular ejection fraction (LVEF>35%) for Sudden Cardiac Death. Abstract No. 102 in ICPES, 14th Congress, *Pacing Clin Electrophysiol* 2011;34:1307.
12. Breithardt G, Cain ME, El Sherif N, et al. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography: a statement by a task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol* 1991;17:999-1006.
13. Gatzoulis KA, Carlson MD, Biblo LA, et al. Time domain analysis of the signal averaged electrocardiogram in patients with a conduction defect or a bundle branch block. *Eur Heart J* 1995;16:1912-1919.
14. Lang R, Bierig M, Richard B, et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79-108.
15. Heart Rate Variability. Standards of measurements, physiological interpretation and clinical use. Task Force of the ESCAR-DIO and the NASPE. *Eur Heart J* 1996;17:354-381.
16. Arsenos P, Gatzoulis KA, Dilaveris P, et al. The rate-corrected QT interval calculated from 24-hour Holter recordings may serve as a significant arrhythmia risk stratifier in heart failure patients. *Int J Cardiol* 2011;147:321-323.
17. Technische Universität München, Working Group of Biological Signal Analyses: http://www.librasch.org/prsa
18. Zaman S, Narayan A, Thiagalingam A, et al. Long-term arrhythmia-free survival in patients with severe left ventricular dysfunction and no inducible ventricular tachycardia after myocardial infarction. *Circulation* 2014;129:848-854.
19. Bauer A, Kantelhardt JW, Bunde A, et al. Phase-rectified signal averaging detects quasi-periodicities in non-stationary data. *Physica A* 2006;364:423-434.
20. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. *Circulation* 1984;69:790-800.
21. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;285:877-883.
22. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium. Influences of heart rate and vagal stimulation. *Circulation* 1973;47:291-298.
23. Ellenbongen KA, Smith ML, Eckberg DL. Increased vagal cardiac nerve traffic prolongs ventricular refractoriness in patients undergoing electrophysiology testing. *Am J Cardiol* 1990;65:1345-1350.
24. Hauptman PJ, Schwartz PJ, Gold MR et al. Rationale and study design of the increase of vagal tone in heart failure study: INOVATE-HF. *Am Heart J* 2012;163:954-962.
25. Arsenos P, Gatzoulis KA, Dilaveris P, et al. Arrhythmia Prediction Trial (APRET). *ClinicalTrials.gov.* Identifier: NCT02175836.
26. Zabel M. An Arrhythmia Risk Predictor Trial. *ClinicalTrials.gov.* Identifier: NCT02010515.
27. Gatzoulis K, Tsiachris D, Arsenos P, et al. Risk Stratification in post Myocardial infarction Patients With Preserved Ejection Fraction (PRESERVE-EF). *ClinicalTrials.*gov. Identifier: NCT02124018.
28. Arsenos P, Gatzoulis KA, Dilaveris P, et al. Deceleration capacity of heart rate: Improvement of the algorithm. Risk stratification for serious arrhythmic events. Poster 7/136 in Cardiostim 2014. *Europace* 2014;16(suppl 2):ii94.
29. Ellenbogen KA, Levine JH, Berger RD, et al. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;113:776-782.