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Risk prediction in post-infarction patients with moderately reduced left ventricular ejection fraction by combined assessment of the sympathetic and vagal cardiac autonomic nervous system

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ABSTRACT

Aim: Most deaths after myocardial infarction (MI) occur in patients with normal or moderately reduced left ventricular ejection fraction (LVEF > 35%). Periodic repolarization dynamics (PRD) and deceleration capacity (DC) are novel ECG-based markers related to sympathetic and vagal cardiac autonomic nervous system activity. Here, we test the combination of PRD and DC to predict risk in post-infarction patients with LVEF > 35%.

Methods and results: We included 823 survivors of acute MI with LVEF > 35%, aged ≤80 years and in sinus rhythm. PRD and DC were obtained from 30-min ECG-recordings within the second week after index infarction and dichotomized at established cut-off values of ≥5.75 deg^2 and ≤2.5 ms, respectively. Patients were classified as having normal (CAF 0), partly abnormal (DC or PRD abnormal; CAF 1) or abnormal cardiac autonomic function (DC and PRD abnormal; CAF 2). Primary endpoint was 5-year all-cause mortality. Within the first 5 years of follow-up, 51 patients died (6.2%). PRD and DC effectively stratified patients into low-risk (CAF 0; n = 562), intermediate-risk (CAF 1; n = 193) and high-risk patients (CAF 2; n = 68) with cumulative 5-year mortality rates of 2.9%, 9.4% and 25.2%, respectively ($p < 0.001$). On multivariable analyses, CAF was independent from established risk factors (GRACE-score, diabetes mellitus, mean heart rate, heart rate variability). Addition of CAF significantly improved the model (increase of C-statistics from 0.732 (0.651–0.812) to 0.777 (0.703–0.850), p = 0.047; continuous NRI (0.400, 95% CI 0.230–0.560, $p < 0.001$); IDI (0.056, 95% CI 0.022–0.122, $p < 0.001$)).

Conclusion: CAF identifies new high-risk post-MI patients with LVEF > 35% which might benefit from prophylactic strategies.

1. Introduction

Survivors of an acute myocardial infarction (MI) face an increased risk for cardiovascular complications including development of malignant arrhythmias, progression of heart failure, myocardial infarction and death [1]. Most preventive strategies such as prophylactic implantation of a cardioverter defibrillator focus on post-infarction patients with reduced left ventricular ejection fraction (LVEF ≤ 35%). However, most deaths after MI occur in patients in whom left ventricular ejection fraction is not particularly compromised (LVEF > 35%) [1–3]. Accurate identification of high-risk individuals in post-MI patients with LVEF > 35% is of crucial importance to guide prophylactic interventions and reduce mortality. This is currently considered to be an unmet clinical need.

Experimental and clinical studies indicated that important prognostic information can be derived from the functional status of the cardiac autonomic nervous system [4–6]. Sympathetic overactivity and loss of vagal tone have been independently associated with adverse events after myocardial infarction [7–9]. Recently, we identified sympathetic-activity associated low-frequency oscillations of cardiac repolarization which we termed periodic repolarization dynamics (PRD) [10]. Increased PRD has been shown to be associated with poor outcome in patients after myocardial infarction and stable coronary artery disease [10] as well as in patients with severely impaired LVEF [11]. Deceleration capacity (DC) of heart rate quantifies predominantly vagally mediated oscillations of heart rate, with low DC indicating increased risk of adverse events [12]. It is plausible to assume that patients with abnormalities of both branches of the cardiac autonomic nervous system are at highest

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risk. Here, we test the usefulness of a combined risk assessment by means of PRD and DC in post-infarction patients with LVEF >35%.

2. Methods

2.1. Patients

The present study is a post-hoc analysis of the Autonomic Regulation Trial [13]. The study included 823 survivors of acute MI with LVEF >35% in sinus rhythm and aged ≤80 years. Fig. S1 shows the flow chart of patient selection. Patients were enrolled at two university hospitals (German Heart Centre and Klinikum Rechts der Isar, both TU Munich, Germany) between March 2000 and May 2005; last follow-up was performed on May 2010. LVEF was assessed by angiography or biplane echocardiography per Simpson's method within the second week (median 7 days, inter-quartile range (IQR) 5–9 days) after the index MI. The study was approved by the institutional ethical committee.

2.2. Assessment of DC and PRD

PRD and DC were assessed from 30-min high-resolution (1.600 Hz) resting ECGs (TMS; Porti System) according to previously published technologies [10,12]. Recordings were performed within the second week after index infarction in supine position under standardized conditions. The details of both technologies have been described elsewhere [10,12,14]. Fig. S2 shows the scheme of DC and PRD calculation.

Briefly, PRD refers to low frequency modulations of cardiac repolarization instability. To calculate PRD, the spatiotemporal characteristics of each T-wave are mathematically integrated into a single vector $T°$, defining the main direction of the T-wave in space. The instantaneous degree of repolarization instability is estimated by the angle $dT°$ between two successive repolarization vectors. The $dT°$-signal typically exhibits low-frequency (≤0.1 Hz) oscillations that are quantified by means of a continuous wavelet transformation [10].

Computation of DC is based on the transformation of the RR-interval time series by a novel signal processing technology termed Phase-Rectified Signal Averaging (PRSA). RR intervals that are longer than their respective preceding RR interval are identified (so-called anchors). Segments around anchors are averaged to obtain the so-called PRSA-signal. The PRSA-signal can be considered as a condensed version of the original RR-interval time series, including all periodic components of heart rate variability related to decelerations. The central part of the PRSA-signal is quantified by wavelet-analysis to obtain the numerical measure of DC. Thus, DC is an integral measure of all deceleration-related oscillations that take place during the observational period [12]. PRD and DC were dichotomized at established cut-off values, with PRD ≥5.75 deg^2 and DC ≤2.5 ms indicating high risk [10,12].

2.3. Classification of cardiac autonomic function (CAF)

According to PRD and DC patients were classified in three groups of cardiac autonomic function (CAF): normal (CAF 0: PRD <5.75 deg^2 and DC >2.5 ms), partly abnormal (CAF 1: PRD ≥5.75 deg^2 or DC ≤2.5 ms) and abnormal (CAF 2: PRD ≥5.75 deg^2 and DC ≤2.5 ms).

Table 2
Statistical association of risk variables with 5-year mortality.

Risk variable	All patients (n = 823)	Survivors (n = 772)	Non-survivors (n = 51)	p
Age (IQR), years	61 (17)	60 (17)	68 (13)	<0.001
Diabetes, n (%)	157 (19.1)	137 (17.7)	20 (39.2)	<0.001
GRACE score (IQR)	109 (32)	108 (33)	126 (25)	<0.001
LVEF (IQR), %	54 (14)	55 (13)	52 (14)	0.192
DC (IQR), ms	4.9 (4.0)	5.0 (3.9)	2.6 (4.1)	<0.001
PRD (IQR), deg^2	2.66 (3.98)	2.57 (3.73)	5.84 (7,91)	<0.001
CAF 0, n (%)	562 (68.3)	546 (70.1)	16 (31.4)	<0.001
CAF 1, n (%)	193 (23.5)	175 (22.7)	18 (35.3)	0.039
CAF 2, n (%)	68 (8.3)	51 (6.6)	17 (33.3)	<0.001
MHR (IQR), bpm	64 (11)	63 (12)	70 (13)	0.001
SDNN (IQR), ms	93 (39)	94 (39)	81 (39)	<0.001

CAF cardiac autonomic function; DC deceleration capacity; GRACE Global Registry of Acute Coronary Events; IQR inter-quartile range; LVEF left ventricular ejection fraction; MHR mean heart rate; PRD periodic repolarization dynamics; SDNN standard deviation of NN intervals.

2.4. Other risk markers

Mean heart rate (MHR) and standard deviation of all normal-to-normal intervals (SDNN) were calculated according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [15] and dichotomized at previously established cut-off values of 75 bpm and 70 ms, respectively [10,12,16].

We also estimated the GRACE score proposed for the prediction of long-term prognosis [17]. The GRACE score combines eight factors (age of the patient, heart rate at admission, systolic blood pressure at admission, Killip classification, serum creatinine at admission, ST-segment deviation at admission, cardiac arrest at admission, cardiac biomarker status at admission). The GRACE score's dichotomy was set at 120, optimizing the separation between high- and low-risk cases (log-rank optimization) as no independent guidance for prospective dichotomy is available.

2.5. Statistical analyses

Continuous variables are presented as median and interquartile range, and qualitative data are expressed as percentages. Primary endpoint was 5-year total mortality. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses were performed using the Cox proportional-hazards model. The effects of the factors investigated are given as hazard ratios with 95% confidence intervals (CI). Tests in the Cox model and log-rank tests were 2-sided. To test the incremental prognostic value of CAF on top of established risk predictors we implemented C-statistics, integrated discrimination improvement (IDI) score and continuous net reclassification improvement analysis (NRI) [18]. To test for differences between C-statistics, bootstrapping

Table 1
Patients' characteristics.

	All patients	Patients with LVEF ≤35%	Patients with LVEF >35% (study population)				
			All study patients	CAF 0	CAF 1	CAF 2	p
Study characteristics							
Number of patients, n	908	85	823	562	193	68	
Total deaths, n (%)	69 (7.6)	18 (21.2)	51 (6.2)	16 (2.8)	18 (9.3)	17 (25.0)	<0.001
Cardiovascular deaths, n (%)	36 (4.0)	11 (12.9)	25 (3.0)	8 (1.4)	9 (4.7)	8 (11.8)	<0.001
Patients' characteristics							
Median age (IQR), years	61 (17)	64 (16)	61 (17)	58 (17)	65 (16)	68 (10)	<0.001
Females, n (%)	174 (19.2)	13 (15.3)	161 (19.6)	107 (19.0)	41 (21.2)	13 (19.1)	0.798
Diabetes mellitus, n (%)	179 (19.7)	22 (25.9)	157 (19.1)	95 (16.9)	41 (21.2)	21 (30.9)	0.015
Median LVEF (IQR), %	53 (15)	30 (13)	54 (14)	55 (15)	53 (14)	51 (14)	0.001
History of prev. MI, n (%)	84 (9.3)	17 (20.0)	69 (8.4)	40 (7.1)	18 (9.3)	11 (16.2)	0.034
NYHA status							
NYHA I	860 (93.2)	78 (91.8)	782 (95.0)	543 (96.6)	178 (92.2)	61 (89.7)	0.006
NYHA II	31 (3.4)	5 (5.9)	26 (3.2)	13 (2.3)	10 (5.2)	3 (4.4)	0.120
NYHA III	5 (0.6)	0 (0)	5 (0.6)	2 (0.4)	3 (1.6)	0 (0)	0.145
NYHA IV	12 (1.3)	2 (2.4)	10 (1.2)	4 (0.7)	2 (1.0)	4 (5.9)	0.001
Treatment							
PCI, n (%)	848 (93.4)	82 (96.5)	766 (93.1)	534 (95.0)	172 (89.1)	60 (88.2)	0.005
Thrombolysis, n (%)	153 (16.9)	11 (12.9)	142 (17.3)	109 (19.4)	30 (15.5)	3 (4.4)	0.007
CABG, n (%)	17 (1.9)	2 (2.4)	15 (1.8)	7 (1.2)	5 (2.6)	3 (4.4)	0.121
Beta blockers, n (%)	865 (95.3)	85 (100)	780 (94.8)	537 (95.6)	179 (92.7)	64 (94.1)	0.310

CABG, coronary artery bypass graft; CAF, cardiac autonomic function; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.