International Journal of Cardiology 224 (2016) 473–481

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Functional parameters but not heart rate variability correlate with long-term outcomes in St-elevation myocardial infarction patients treated by primary angioplasty

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ARTICLE INFO

Article history:
Received 24 June 2016
Received in revised form 19 September 2016
Accepted 20 September 2016
Available online 23 September 2016

Keywords:
Heart rate variability
Physical fitness
Cardiopulmonary exercise test
Primary percutaneous coronary intervention
Myocardial infarction
Prognosis

ABSTRACT

Background: Depressed heart rate variability (HRV) is usually considered a negative long-term prognostic factor after acute myocardial infarction. Anyway, most of the supporting research was conducted before the era of immediate reperfusion by percutaneous coronary intervention (PCI). Main aim of this study was to evaluate if HRV still retains prognostic significance in our era of immediate PCI.

Methods and results: Two weeks after STEMI treated by primary PCI, time-domain HRV was assessed from 24-h Holter recordings in 186 patients: markedly depressed HRV (SDNN <70 ms or <50 ms) was present in 16% and in 5% of cases, respectively; patients with left ventricle ejection fraction (LVEF) <40% presented more often SDNN values in the lowest quartile. Physical performance was also assessed, by 6-minute walk tests (6MWT) and by cardiopulmonary exercise test (CPET). After >2 years from infarction, occurrence of major clinical events (MCE) was investigated. Cases with or without MCE did not differ by initial HRV parameters; Kaplan–Meier events-free survival curves were similar between patients with lowest quartile SDNN and the remaining ones (χ^2 0.981, $p = 0.322$). By the contrary, events-free survival was worse if patients walked shorter distances at 6MWT (χ^2 6.435, $p = 0.011$), developed poorer ventilatory efficiency at CPET (χ^2 10.060, $p = 0.002$), or presented LVEF <40% (χ^2 7.085, $p = 0.008$).

Conclusions: In primary-PCI STEMI patients, markedly abnormal HRV was found in a small percentage of cases. HRV seems to have lost its prognostic significance, while parameters indicating LV function (LVEF and physical performance) could allow better prognostication in primary-PCI STEMI patients.

List of acronyms

%-VO_2	percentage of expected peak Oxygen uptake
6MWT	6-min Walk Test
ACE	Angiotensin Converting Enzyme
AMI	Acute Myocardial Infarction
AT-II	Angiotensin II receptor type 2
CABG	Coronary Artery By-pass Graft
CPET	Cardio-Pulmonary Exercise Test
CR	Cardiac Rehabilitation
ECG	Electrocardiogram
HRV	Heart Rate Variability
LVEF	Left Ventricle Ejection Fraction
MCE	Major Clinical Events
MRI	Magnetic Resonance Imaging
PCI	Percutaneous Coronary Intervention
peak-VO_2	peak oxygen uptake
RMSSD	Root Mean Square of Successive Differences between Normal-to-Normal intervals
SDANN	Standard Deviation of all 5-min mean Normal-to-Normal intervals
SDANN-i	Mean of the Standard Deviations of all Normal-to-Normal intervals of all 5-min segments in the 24 h
SDNN	Standard Deviation of all Normal-to-Normal intervals
STEMI	ST-elevation Myocardial Infarction

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http://dx.doi.org/10.1016/j.ijcard.2016.09.070

VE/VCO_2 slope ventilatory efficiency (minute ventilation-carbon dioxide production relationship)
W-max maximum sustained workload at CPET, in Watt

A marked reduction of heart rate variability (HRV) indicating profound derangement of the cardiac autonomic system has been often described in the past in patients after an acute myocardial infarction (AMI). The presence of such abnormality of HRV has been considered as a powerful predictor of poor long-term prognosis, [1–2] especially among high risk and complicated patients. [3].

Anyway, the majority of the studies showing a correlation between reduced HRV and clinical outcomes after an AMI have been conducted before the era of immediate reperfusion by percutaneous coronary intervention (PCI). In a recent review by Brateanu et al., [4] among the 21 reported studies only in 5 studies patients had been treated by primary PCI, although in a widely variable percentage of cases (ranging from 18% up to 95% of cases). [5–6].

More recently, a few other small scale studies have been published on limited number of patients, analyzing the prognostic value of HRV in ST-elevation myocardial infarction (STEMI) patients treated by primary PCI. [7–8] In these studies, conducted on patients treated by primary PCI on the culprit coronary artery, severely depressed SDNN (i.e. <70 ms) is reported to be present with incidences that vary between 21% and 34% of cases. [9] Such incidence seems even greater than that reported in studies conducted in the pre-primary-PCI era, such as the GISSI-2 or the ATRAMI studies, where SDNN <70 ms was reported in 15% of patients, [2,10] and contrasts with the much lower prevalence of 7% reported by Erdogan et al., that anyway fixed the cut-off of SDNN at <50 ms. [6] So actual prevalence of depressed HRV in contemporary primary-PCI-treated post-AMI patients is not really clear.

All the studies, anyway, confirm what observed in the previous large study by Huikuri et al., [11] that reduced HRV still retains negative predictive value on short and long-term prognosis; HRV parameters possess high specificity (even though poor sensibility), that is greater than that provided by left ventricle ejection fraction (LVEF). [12].

An additional fact to be considered is that nowadays an increasing number of post-AMI patients are admitted to a cycle of cardiac rehabilitation (CR), [13] mainly based on exercise training. Besides positive effects on cardiovascular mortality, [14–15] CR may exert some positive effects on cardiac autonomic function, as reported in experimental [16] and clinical studies, although there is no unanimous consensus on this issue. [17–24].

Thus, the complex interrelationship between cardiac autonomic system and exercise-based rehabilitation (with the related improvement of physical fitness), and the influence of these factors on long-term survival of post-primary-PCI patients constitute a changing scenario.

Aims of this study were: 1- to assess the prevalence of severely decreased HRV in patients admitted to CR after a complicated STEMI treated by primary PCI, 2- to evaluate if HRV still maintains a prognostic value in the era of immediate reperfusion in patients submitted to CR, 3- to estimate possible relationship between HRV and physical fitness.

1. Materials and methods

1.1. Design of the study

We retrospectively reviewed the clinical files of 236 consecutive patients, that were part of a larger study on the effects of CR after AMI. They had all suffered a first event of complicated STEMI and had been admitted to our CR unit for a period of residential, exercise-based rehabilitation, a median of 13.0 days (95% CI of the median: 11.6–14.4) after the index event. All patients had undergone coronary angiography at initial admission to the Intensive Coronary Care Unit, during the first 6 h from beginning of AMI symptoms: 94% of them underwent PCI of the culprit coronary artery, while only a small percentage of them (15 cases, 6%) was not revascularized due to unfavorable coronary anatomy and were put on optimal medical therapy. Patients were selected by the submitting centre and sent to our CR program if they suffered a complicated AMI (cardiogenic shock or pulmonary edema, episode of cardiac arrest, complex ventricular arrhythmias), or if they had incomplete revascularization (because of unfavorable coronary anatomy or technical failure). [25] Low risk patients followed an out-patient CR program in another centre and were not considered for this study.

Echo- or cardiac MRI-documented intracavitary thrombosis, extreme thinning or intra-myocardial bleeding and/or suspected rupture of the ventricular wall were exclusion criteria from admittance to CR. History of previous myocardial infarction was an exclusion criterion for the present study.

The following clinical variables were recorded for each patient: age, gender, body mass index, cardiovascular risk factors, site of infarction, culprit coronary artery vessel, number of diseased coronary artery vessels (defined as presence of diameter stenosis >50%), history of previous PCI or coronary or valvular surgery, presence of ancillary diseases (renal failure, thyroid dysfunction, known diabetes or abnormal glucose metabolism, pulmonary diseases, history or presence of neoplastic diseases, carotid and peripheral vascular disease) and drug therapy. During stay in CR, all patients without previous diagnosis of diabetes underwent an oral glucose tolerance test to identify subclinical abnormal glucose metabolism. Left ventricular ejection fraction (LVEF) was measured before discharge by 2-D echocardiography, following the Simpson method.

1.2. Holter monitoring

On the day of admittance to CR, all patients underwent 24-hour ECG Holter recording, using 3-channel digital recorders (Lifecard CF, Del Mar. Reynolds, Irvine, CA, USA), monitoring the chest leads CM5, CM3, and modified aVF. Recordings were analyzed using a commercial Holter device system (Del Mar-Reynolds Impresario Holter Analysis System, vers. 2.8.0024; Time-domain HRV Analyzer, vers. 1.0.8.4, CENTUM & Del Mar. Reynolds Medical Inc., Irvine, CA, USA; sampling rate: 128 Hz).

After cleansing of arrhythmias and artifacts, the usual time domain HRV variables were assessed: the standard deviation of all normal-to-normal (NN) intervals (SDNN), the standard deviation of all 5-min mean NN intervals (SDANN), the root mean square of successive differences (RMSSD), and mean of the standard deviations of all RR intervals of all 5-min segments in the 24 h (SDNN-i). For the purposes of this study, the main variable that was considered in the correlations with other clinical and functional parameters was SDNN, as it is considered a measure of total variance in heart rate; it is the variable most widely used in previous studies, [4] considered strongly associated with prognosis. [26].

We excluded from the study patients with atrial fibrillation, or rhythm disturbances that could interfere with accurate HRV analysis (e.g. frequent ectopic beats, rhythm induced by pacemaker), and patients with inadequate recordings.

1.3. Cardiac rehabilitation

The training consisted of a low-medium intensity exercise protocol developed in 3 sets of exercises, 6 days a week for an average of 2 weeks: 30 min of respiratory training, followed by an aerobic session on a stationary bike (or with an arm-ergometer for those patients who were not able to cycle) in the morning and 30 min of callisthenic exercises in the afternoon. Each session was supervised by a physician and a physiotherapist and all patients were ECG monitored by a telemetry system. Aerobic training was performed using a constant work rate modality, without exceeding 70% of the maximal predicted peak heart rate for each patient. [27] Each aerobic session lasted 10 min at the beginning, with a 5 min progressive increase to reach a 30 min target; the exercise prescription and evaluation of exercise intensity was carefully derived from the subjective rating of perceived exertion, using a category ratio Borg scale.

Individual and group counseling meetings and nutritional evaluation were also performed for all patients.

1.4. Physical evaluation

Physical performance of the patients was assessed by two different methods: two six-minute walk tests (6MWT), performed at admission (6MWT-in) and at the end of the rehabilitative period (6MWT-out), and a symptom-limited cardiopulmonary exercise test (CPET) performed on the day before discharge from CR.

The 6MWTs were performed in a 30 m long, unobstructed indoor corridor, according to the American Thoracic Society recommendations. [28]

The CPET was performed on a computer-driven cycle ergometer (Cardiovit CS-200 Ergo-Spiro, Schiller AG, Baar, CH; Ergoselect 100 ergometer, Ergoline GmbH, Bitz, D). A progressive ramp protocol of 6 to 10 W/min was used, until subjective exhaustion or appearance of clinical or electrocardiographic criteria for termination. [29] Expired gas was collected by means of a tightly fitting face mask and continuously analyzed during the exercise test (Schiller Ganshor CS-200 Power Cube). Peak oxygen consumption (peak-VO_2) was expressed relative to body weight, and as percentage of the expected based on age, sex and body mass (%-VO_2). Peak exercise capacity was expressed in Watt as maximum sustained workload (W-max). The ventilatory efficiency was calculated based on the slope of ventilation (VE) related to carbon dioxide production (VCO_2) during the aerobic phase of the exercise (VE/VCO_2 slope). [30].

1.5. End points and follow-up

At the time of follow-up, the clinical status of the patients was assessed by telephone interviews, performed by a doctor or a trained team nurse. In case of clinical events,