ELSEVIER

International Journal of Cardiology 134 (2009) 67–74

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Long-term prognostic value of heart-rate recovery after treadmill testing in patients with diabetes mellitus

Panagiotis Georgoulias [a,*], Nikolaos Demakopoulos [b], Varvara Valotassiou [a], Alexandros Orfanakis [c], Alexia Zaganides [a], Ioannis Tsougos [d], Ioannis Fezoulidis [a]

[a] *Department of Nuclear Medicine, Medical School, University of Thessaly and University Hospital of Larissa, Larissa, Greece*
[b] *Department of Nuclear Medicine, NIMTS Hospital, Athens, Greece*
[c] *Department of Cardiology, University Hospital of Heraklion, Heraklion, Greece*
[d] *Department of Medical Physics, Medical School, University of Thessaly, Larissa, Greece*

Received 24 June 2007; received in revised form 17 October 2007; accepted 14 January 2008
Available online 21 May 2008

Abstract

Background: Heart-rate recovery (HRR) is considered to be an independent predictor of cardiac and all-cause mortality. We examined the long-term prognostic value of HRR in patients suffering from diabetes mellitus.
Methods: In this study, we included 258 consecutive patients. Patients whose HRR value or myocardial perfusion imaging could have been influenced by factors other than myocardial ischaemia, were excluded. The value of HRR was defined as the decrease in the heart-rate from peak exercise to 1 min after the termination of the exercise. All patients underwent SPECT myocardial perfusion imaging combined with exercise testing. Cardiovascular death and non-fatal myocardial infarction were considered as hard cardiac events, while late revascularization procedures as soft events. Cox proportional-hazard models were applied to evaluate the association between HRR and the investigated outcome.
Results: During the follow-up period (30.8±6.9 months), hard cardiac events occurred in 21 (8%) patients (15 with abnormal HRR value, $p<0.001$), while 35 (14%) patients underwent revascularization (31 with abnormal HRR value, $p<0.001$). Considering it as a continuous variable, HRR was a strong predictor for both hard cardiac (coefficient=−0.41, SE=0.052, $p<0.001$) and soft cardiac events (coefficient=−0.63, SE=0.058, $p<0.001$). After adjustments were made for potential confounders, including scintigraphic variables, abnormal HRR remained an independent predictor for hard and soft cardiac events ($p<0.001$).
Conclusion: Our results suggest that among patients with diabetes, a decreased HRR is a significant independent predictor of hard and soft cardiac events.

Keywords: Heart-rate recovery; Diabetes; Treadmill testing; Myocardial SPECT; Prognosis

1. Introduction

The rise in heart-rate during exercise is considered to be due to a combination of parasympathetic withdrawal and sympathetic activation, whereas the decline in heart-rate immediately after exercise has been proposed to be a function of the reactivation of the parasympathetic tone [1–3].

The autonomic nervous system is responsible for significant influences on myocardial pathophysiology, while autonomic neuropathy is a common complication in diabetic patients and particularly in those using insulin [4,5].

The pathophysiology of abnormal heart-rate recovery (HRR) involves the inability to slow down the heart-rate

* Corresponding author. 15 Kritis St. 19009 Rafina, Greece. Tel.: +30 22940 26201, +30 2410 682052; fax: +30 22940 78400, +30 2410 670117.
E-mail addresses: pgeorgoul@med.uth.gr, georgoulias@hotmail.com (P. Georgoulias).

0167-5273/$ - see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2008.01.036

immediately after exercise, which has been previously shown to be a marker of decreased vagal activity. Attenuated HRR after exercise testing has been found to be an independent predictor of cardiac mortality in patients referred for exercise electrocardiogram [6–11]. Although diabetes mellitus is associated with increased mortality from cardiovascular disease, only few published data have engaged with the predictive value of a decreased HRR in diabetic patients [11–13].

The aim of this study was to evaluate the usefulness of HRR after treadmill testing as a long-term prognostic marker of cardiovascular morbidity and mortality in diabetic patients, in comparison to the prognostic value of exercise testing and myocardial single photon emission computed tomography (SPECT) variables.

2. Materials and methods

2.1. Population

The study cohort consisted of 258 consecutive diabetic patients (168 men and 90 women) ranging in age from 33 to 81 years (mean age 55.69±11.24 years), who were properly referred (based on their data), between May 2002 and December 2004, for a symptom-limited exercise testing combined with a SPECT myocardial perfusion imaging, for the evaluation of known or suspected coronary artery disease and patient risk stratification (Table 1). All patients were suffering from diabetes mellitus according to the American Diabetes Association criteria [14]. Only patients using hypoglycemic medication were included in the study; 109 patients were using insulin and 149 were using oral hypoglycemic agents (Table 1).

We excluded pregnant women, patients with a history of heart failure, left bundle branch block, pre-excitation syndromes, atrioventricular block or known sick sinus syndrome, with atrial fibrillation or other tachyarrhythmias, with bradycardia, those with a history of prior myocardial infarction or a completely irreversible (permanent) defect in their scintigram, previous cardiac surgery (bypass grafting or angioplasty), congenital or valvular heart disease, patients with cardiomyopathy and those with an implanted pacemaker. We also excluded patients taking digoxin or amiodarone (due to their prolonged chronotropic effect) and those with contraindication to or inability to perform treadmill testing or to achieve a satisfactory exercise level because of an exocardiac condition (peripheral vascular disease, sciatica, neuropathy, disability etc.).

Table 1
Characteristics of the study group in comparison to heart-rate recovery value.

Characteristic	Normal HRR (≥21 bpm)	Abnormal HRR (<21 bpm)
Number of patients	179	79
Age (years)	51±13	63±11***
Sex (male) — no. (%)	108 (60%)	60 (76%)**
Smoking — no. (%)	77 (43%)	53 (67%)***
Obesity — no. (%)	62 (35%)	41 (52%)**
Hypertension — no. (%)	87 (49%)	48 (61%)*
Lipid disorder — no. (%)	103 (58%)	69 (87%)***
Glucose (mg/dl)	118±6	135±9***
Use of insulin — no. (%)	61 (34%)	42 (53%)**
Use of β-blockers — no. (%)	33 (18%)	31 (39%)**
Use of calcium – channel antagonists – no. (%)	37 (21%)	35 (44%)***
Use of nitrates — no. (%)	29 (16%)	34 (43%)***
Use of other antiarrhythmics — no. (%)	3 (0.016%)	2 (0.025%)

HRR, heart-rate recovery; bpm, beats per minute.
*$p<0.05$, **$p<0.01$, ***$p<0.001$.

Medications that could possibly influence patient performance on exercise testing and the related variables, were temporarily withdrawn (for about five half-lives). β-blockers were discontinued gradually (within a week — depended on the medication and the dose), with complete discontinuation at least 48 h before and during the study. Calcium channel antagonists and nitrates were discontinued 48 and 24 h before and during the study, respectively. Other antiarrhythmic medications were also discontinued (at least 48 h before and during the study, according to medication half half-life). Additionally, any patient whose medication had not been discontinued as described above was excluded. Finally, patients who were lost to follow-up or died of a non-cardiovascular cause during follow-up and those who underwent early revascularization (<3 months after myocardial SPECT: 12 CABG and 10 PCI), were excluded from the prognostic analysis.

Before testing, all patients gave informed consent for their participation, according to the Hospital Ethics Committee guidelines (based on the ethical guidelines of the 1975 Declaration of Helsinki), and a brief structured interview during which we obtained data on symptoms, medications, previous cardiac events, coronary risk factors and cardiac or non-cardiac diagnoses.

All patients had fasting blood glucose measurements taken prior to the study. Hypertension was considered as a systolic blood pressure of 140 mm Hg or greater at rest and/or a diastolic blood pressure of 90 mm Hg or greater at rest, or treatment with antihypertensive medicines. Diagnoses of lipid disorders were derived from the interviews with the patients and the use of relevant medications. Obesity was considered as a body mass index (BMI — calculated as weight in kilograms divided by height in meters squared) of 30.0 or greater.

Prior to the study, patients were also given written directions on radioprotection.

2.2. Follow-up

Follow-up data were obtained by phone contact with the patients, their relatives and patients' general practitioner or cardiologist, during visits to the clinic and/or review of the patients' hospital records. Cardiovascular death and non-fatal myocardial infarction were considered as hard cardiac events, while revascularization (≥3 months after myocardial