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Original article

Prognostic significance of heart rate recovery in patients with diabetes mellitus and silent ischemia

Predrag Jancic[1], Emilija Jancic,[1] Vojislav Giga,[1,2] Nikola Boskovic[2], Marko Banovic[1,2]

[1]*Faculty of Medicine, University of Belgrade,* [2]*Cardiology Clinic, Univeristy Clinical Center of Serbia*

Abstract

Introduction: Heart rate recovery (HRR) after stress testing is an indicator of normal vagal activity which is in relation to the risk of premature death. Therefore, the prognostic value of this parameter for adverse events needs to be investigated, especially in patients with diabetes whose heart innervation is often disturbed.

Methods: The research included 112 patients. The patient follow-up was performed via telephone interview. Patients were divided into groups with and without silent ischemia. Four major adverse events (MACE) were investigated: myocardial revascularization, heart failure with hospitalization, heart attack and all-cause death. Median follow up time was 5 years.

Results: Patients with silent ischemia had significantly lower HRR compared to patients without it (22.8 ± 10.4 vs. 29.4 ± 13.8 beats per minute, p=0.031). The risk of MACE was significantly higher in patients with silent ischemia compared to patients without it (54.2% vs. 25%, p=0.006), with patients with silent ischemia having 2.88 times higher incidence of MACE during long-term follow-up (HR 2.882; 95% CI 1.449-5.174; p=0.03). The group of patients with slow HRR had almost 2 times higher incidence of MACE during long-term follow-up in comparison to the group of patients with normal HRR (HR 1.918; 95%CI: 0.939-3.916; p=0.074).

Conclusion: Patients with diabetes and silent ischemia had significantly higher risk of MACE compared to patients without silent ischemia during long-term follow-up. To determine the importance of HRR in adverse event prediction in patients with silent ischemia, further research is needed with a larger number of patients.

Kew words stress-echocardiography test, diabetes mellitus, miocardial ishemia

Introduction

Coronary artery disease represents the leading cause of death in patients with type 2 diabetes mellitus.[1] The prognosis of diabetes is worsened by cardiovascular complications, which are more frequent and with more severe manifestations in these patients than ones without diabetes.[1,2] especially in the developing countries. Diabetes is a major cardiovascular risk factor; it often leads to severe cardiovascular complications, and coronary artery disease (CAD Myocardial ischemia is defined as a disturbed ratio of oxygen demand and supply during resting and/or during exertion, which manifests as haemodynamic (kinetic changes), metabolic (lactic production), electrical (repolarisation) and clinical (chest pain) consequences. Silent ischemia is defined as an absence of clinical symptoms during ischemia[2] especially in the developing countries. Diabetes is a major cardiovascular risk factor; it often leads to severe cardiovascular complications, and coronary artery disease (CAD It has been shown to occur in approximately 20% of asymptomatic patients with type 2 diabetes and early diagnosis is a crucial step in treatment.[3]

One of the explanations as to why a certain group of patients with a confirmed myocardial ischemia exibits symptoms while the other doesn't is that patients with diabetes, due to peripheral neuropathy and autonomous dysregulation, show an elevated threshold for pain stimuli. In addition, there is evidence that the pain receptors in the myocardium themselves are being qualitatively and quantitatively changed.[4]

Increase in heart rate during physical activity is a phenomenon coordinated by simultaneous activation of sympathetic and decrease in parasympathetic function.[5] Heart rate recovery (HRR) immediately after exercise is a process driven by the tone of the vagal nerve and its activation during resting. Adequate vagal tone is associated with a lower risk of premature death of all causes.[6] Therefore HRR, as a function of the vagal activity, can be used in risk stratificaton for premature cardiac death, as well as death from other causes.

The aim of our paper was to investigate the prognostic importance of HRR after physical or pharmacological stress testing in patients with diabetes, as well as the importance of silent ischemia occurring during and/or after stress testing for the occurrence of adverse cardiovascular events.

Address for correspondence: Dr Predrag Jancić, Mostarska 43, 11300 Smederevo. E.mail: prjancic@gmail.com

Methods

Patients who had undergone a stress test in the Cardiology Department in the Clinical Center of Serbia in a period from January to May 2015 were identified retroactively through data acquired from the Polyclinic stress-echocardiography database. All of the subjects were diabetic. The diagnosis of diabetes was confirmed either by reviewing the documentation or on the basis of taking medication for the treatment of diabetes. Patient follow-up lasted 5 years. Four main events followed in the research were: myocardial revascularization (either percutaneous or surgical), heart failure hospitalization, heart attack and a fatal outcome from all-cause. Therefore, events were grouped into "major cardiac adverse events" (MACE) which encompassed first three events and "all adverse events" which encompassed all four. Information about these events was acquired through direct contact with patients via telephone interview. For those patients who experienced adverse events documentation was requested.

Stress electrocardiography and echocardiography

The test was performed according to the standard Bruce protocol or the modified Bruce protocol on a treadmill, as was previously defined.[7] A widely used treadmill testing tool, is a weighted index combining exercise time or capacity, maximum ST-segment deviation and exercise-induced angina. No previous studies have investigated whether the Duke treadmill score and its individual components based on bicycle exercise testing predict cardiovascular death. Design: Two populations with a standard bicycle testing were used: 3936 patients referred for exercise testing (2371 men, age 56 ± 13 years Moreover, we included patients who had undergone the dobutamine testing in doses 10, 20 and 40 mcg/kg/min.[8] The pharmacological stress test was performed until the submaximal heart rate was achieved, or otherwise until the last dose of 40 mcg/kg/min ran out.

Diagnostic end-points of stress echocardiography are: maximal dose (in pharmacological testinig) or maximal workload (in exercise testing); achievement of target heart rate; severe chest pain; obvious echocardographic positivity (with akinesia of ≥ 3 left ventricular segments); obvious electrocardiographic positivity (with > 2mV ST segment shift). Submaximal nondiagnostic end-points of stress echo testing are intolerable symptoms or limiting asymptomatic side effects (hypertension, hypotension, supraventricular arrhythmias and complex ventricular arrhythmias).[9]

Patients were advised to stop taking beta blockers 24 hours prior to testing, considering they can affect the heart rate during testing, as well as ECG and ECHO findings.[10] by correlating heart rate recovery with known parameters of myocardial ischemia. Methods and Results. Included in the study were 304 consecutive patients (73% men

The level of physical effort was estimated by MET (metabolic equivalent) where 1 MET represents the amount of energy needed to burn 3,5ml of oxygen per kilogram per minute while resting.

The Duke score was calculated according to the formula: Duration of test – (5x maximal ST change in millimeters) – (4x angina index). The angina index has a value of 0 (no chest pain caused by exercise), 1 (pain that doesn't affect the ability to exercise) and 2 (pain that affects the ability to exercise).[7] a widely used treadmill testing tool, is a weighted index combining exercise time or capacity, maximum ST-segment deviation and exercise-induced angina. No previous studies have investigated whether the Duke treadmill score and its individual components based on bicycle exercise testing predict cardiovascular death. Design: Two populations with a standard bicycle testing were used: 3936 patients referred for exercise testing (2371 men, age 56 ± 13 years

Before starting the test, as well as after every phase of testing, the heart rate, systolic and diastolic pressure were measured, and the ECG and ECHO findings were read. One minute after the test was concluded heart rate was measured. HRR was calculated as the difference between the biggest value measured during testing and the value measured after the first minute of resting. The normal value of HRR is minimum 18 beats per minute.[11] The stress test was considered positive if there were ischemic changes registered on the ECG (ST depression or elevation ≥ 1mm in two consecutive leads, newly formed T wave changes) and/or worsening of segmental kinetics on the ECHO immediately after stopping the treadmill or during the pharmacological stress test. A positive test for ischemia without patients experiencing any clinical symptoms was considered silent ischemia.

Statistical analysis

Software SPSS for Windows v21.0 (SPSS Inc. Chicago, IL, SAD) was used for the statistical analysis of the collected data. Numerical (continuous) variables were presented as the arithmetic mean ± standard deviation, while the nominal (categorical) variables were presented as absolute frequencies with a percentage share. The Student t test was used for testing numerical variables, while the chi-square test of independence or the Fisher exact test were used for testing categoric variables. A Kaplan-Meier curve with log rank test was used for analyzing the difference in frequency of events between the two tested groups of patients during the follow-up period. The risk rate between the two tested groups of patients was estimated by Cox-regression analysis. Statistical significance was set at $p<0,05$.

Results

A total of 112 patients with positive exercise testing for myocardial ischemia were included in the analysis. Mean age of patients was 63 ± 9 years and 59 (52,7%) of them were male. Forty patients (35,7%) had a history of heart attacks, while 53 (47,3%) patients had a previous myocardial revascularisaton. During stress testing 24 (21,4%) patients had ischemic changes without accompanying symptoms (silent ischemia), while 88 (78,6%) patients had a clincally manifest myocardial ischemia during the test. Other demographic and clinical data of interest can be found in Table 1.

Mean value of HRR for the entire examined population was 27,7 ± 12,1 beats per minute. Patients with silent ischemia had a significantly lower HRR in comparison to patients without silent ischemia (22,8 ± 10,4 vs. 29,4 ± 13,8 beats per minute, p=0,031). BMI and Duke score were significantly lower in the group of patients with silent ischemia compared to the group without it (25,7 ± 3,5 vs. 27,9 ± 3,8 kg/m^2, p=0,013; 3,1 ± 4,1 vs. 6,2 ± 2,8 kg/m^2, p=0,003). Other demographic and clinical characteristics of patients with and without silent ischemia can be found in Table 2.

Major adverse cardiac events and all adverse events were significantly more frequent in patients with silent ischemia comapred to patients without silent ischemia (41,7% vs. 21,6%, p=0,047; 54,2% vs. 25,0%, p=0,006). The group of patients with silent ischemia had a 2,88 times higher risk for all adverse events in the long-term follow-up period compared to the group of patients without silent ischemia (HR 2,88; 95%CI: 1,449-5,174; p=0,03). (Figure 1)

Twenty-four patients had slow HRR (values of 18 beats per minute and lower), 8 (33,3%) with silent ischemia and 16 (18,2%) without silent ischemia. However, statistically significant difference in occurence of slow HRR in patients with silent ischemia compared to the patients without silent ischemia was not observed (p=0,109).

When the examined population was devided according to slow and normal HRR, a group of 24 (21,4%) patients with slow HRR and 88 (78,6%) patients with normal HRR was formed. In the group of patients with normal HRR a more frequent usage of diuretics, nitrates and statins was observed compared to the group of patients with slow HRR (66,7% vs. 27,3%, p<0,001; 54,2% vs. 27,3%, p=0,013; 75,0% vs. 51,1%, p=0,037). In addition, this group achieved the submaximal heart rate during the stress test much more frequently compared to the patients with slow HRR (50,0% vs. 76,7%, p=0,011). No significant difference in all adverse events was shown between these two groups (p=0,082). Demographic and clinical characteristics of patients with slow and normal HRR can be found in Table 3. The group of patients with slow HRR had an almost 2 times higher risk of all adverse events in the long-term follow-up period compared to the group of patients with normal HRR (HR 1,918; 95%CI: 0,939-3,916; p=0,074). (Figure 2)

Table 1. General demographic and clinical characteristics of the patients

Variable	**N=112**
Male gender	59 (52,7%)
Age (years)	63 ± 9
BMI (kg/m^2)	27,2 ± 3,7
Positive family history	58 (51,8%)
Smoker	51 (45,5%)
Hypertension	97 (86,6%)
Diabetes (oral andidiabetics)	54 (42%)
Diabetes (insulin dependant)	16 (14,3%)
Hyperlipoproteinemia	76 (67,9%)
Previous myocardial infarction	40 (35,7%)
Previous revascularization (percutaneous or surgery)	53 (47,3%)
Antiaggregation therapy	76 (6,9%)
β blockers	81 (72,3%)
ACE inhibitors/aldosteron receptor antagonists	67 (59,8%)
Calcium channel blockers	39 (34,8%)
Diuretics	40 (35,7%)
Nitrates	37 (33%)
Statins	63 (56,3%)
Resting heart rate (beats per minute)	77,3 ± 15,2
Systolic blood pressure (mmHg)	124,3 ± 14,3
Diastolic blood pressure (mmHg)	75,3 ± 7,3
Submaximal heart rate (beats per minute)	132,7 ± 7,9
Maximal heart rate during testing (beats per minute)	135,3 ± 1,1
Achieved submaximal heart rate	78 (70,9%)
Maximal systolic blood pressure during testing (mmHg)	158,5 ± 22,9
Maximal diastolic pressure during testing (mmHg)	84,2 ± 6,6
Test duration (min)	6,4 ± 2,2
Duke score	5,6 ± 3,3
MET	7,5 ± 2,3
Heart rate recovery (beats per minute)	27,7 ± 12,1
Slow heart rate recovery	24 (21,4%)
Adverse events	29 (25,9%)

BMI – body mass index; MET – metabolic equivalent of task

Discussion

Our research showed that patients with silent ischemia have a significantly higher number of adverse events in comparison to patients without silent ischemia during stress testing, which is in accordance with some of the previously published studies.(12)”ISSN”:”15583597”,”abstract”:”Myocardial ischemia can occur without overt symptoms. In fact, asymptomatic (or silent We also demonstrated that a statistically significant difference in HRR exists between patients with and without silent ischemia. On the other hand, in patients with inadequate HRR no statistically significant difference in the occurence of MACE was observed between patients with silent ischemia and those without it. This can be explained by the fact that minimal values used for slow HRR vary in literature (13)compare it to other test responses, evaluate its diagnostic value and clarify some of the methodologic issues surrounding its use. BAGKGROUND: Studies have highlighted the value of a new prognostic feature of the treadmill test - rate of recovery of HR after exercise. These studies have had differing as well as controversial results and did not consider diagnostic test characteristics. METHODS: All patients were referred for evaluation of chest pain at two university-affiliated Veterans Affairs Medical Centers who underwent treadmill tests and coronary angiography between 1987 and 1999 were determined to be dead or alive

Table 2. Demographic and clinical characteristics of patients with silent ischemia and patients without silent ischemia

Variable	Patients with silent ischemia (N=24, 21,4%)	Patients without silent ischemia (N=88, 78,6%)	p value
Male gender	16 (66,7%)	43 (48,9%)	0,122
Age (years)	64 ± 10	63 ± 9	0,768
BMI (kg/m^2)	25,7 ± 3,5	27,9 ± 3,8	0,013
Positive family history	12 (50%)	46 (52,3%)	0,843
Smoker	11 (45,8%)	40 (45,5%)	0,974
Hypertension	22 (91,7%)	75 (85,2%)	0,412
Diabetes (oral andidiabetics)	8 (33,3%)	46 (52,3%)	0,100
Diabetes (insulin dependant)	2 (8,3%)	14 (15,9%)	0,347
Hyperlipoproteinemia	18 (75%)	58 (65,9%)	0,398
Previous myocardial infarction	10 (47,1%)	30 (34,1%)	0,492
Previous revascularization (percutaneous or surgery)	11 (45,8%)	42 (47,7%)	0,869
Antiaggregation therapy	15 (62,5%)	61 (69,3%)	0,526
β blockers	16 (66,7%)	65 (73,9%)	0,485
ACE inhibitors/aldosteron receptor antagonists	13 (54,2%)	54 (61,4%)	0,524
Calcium channel blockers	7 (29,2%)	32 (36,4%)	0,512
Diuretics	8 (33,3%)	32 (36,4%)	0,784
Nitrates	9 (37,5%)	28 (31,8%)	0,600
Statins	10 (41,7%)	53 (60,2%)	0,104
Resting heart rate (beats per minute)	74,7 ± 13,0	78,1 ± 15,5	0,330
Systolic blood pressure (mmHg)	128,8 ± 17,8	123,6 ± 13,4	0,126
Diastolic blood pressure (mmHg)	76,7 ± 8,2	75,1 ± 7,1	0,365
Submaximal heart rate (beats per minute)	132,2 ± 8,2	132,9 ± 7,6	0,701
Maximal heart rate during testing (beats per minute)	133,9 ± 15,3	135,2 ± 17,5	0,731
Achieved submaximal heart rate	16 (66,7%)	62 (72,1%)	0,605
Maximal systolic blood pressure during testing (mmHg)	156,3 ± 18,1	158,4 ± 24,4	0,693
Maximal diastolic pressure during testing (mmHg)	85,6 ± 5,8	83,8 ± 6,9	0,248
Test duration (min)	6,4 ± 2,9	6,5 ± 2,2	0,911
Duke score	3,1 ± 4,1	6,2 ± 2,8	0,003
MET	7,7 ± 3,0	7,6 ± 2,2	0,127
Heart rate recovery (beats per minute)	22,8 ± 10,4	29,4 ± 13,8	0,031
Slow heart rate recovery	8 (33,3%)	16 (18,2%)	0,109
All adverse events	13 (54,2%)	22 (25%)	0,006
Major cardiac adverse events	10 (41,7%)	19 (21,6%)	0,047

BMI – body mass index; MET – metabolic equivalent of task

after a mean seven years of follow-up. All-cause mortality was the end point for follow-up, and coronary angiography was the diagnostic gold standard. RESULTS: There were 2,193 male patients who had treadmill tests and coronary angiography. Heart rate recovery at 2 min after exercise outperformed other time points in prediction of death; a decrease of <22 beats/min had a hazard ratio of 2.6 (2.4 to 2.8 95% confidence interval and amongst the diagnostic institutions in which the tests are conducted. This is why certain publications propose that the cut off value for normal HRR should be reduced and more precise reference values should be found for all patients.(5,10,14,15)we hypothesized that a delayed fall in the heart rate after exercise might be an important prognostic marker. METHODS For six years we followed 2428 consecutive adults (mean [+/-SD] age, 57+/-12 years; 63 percent men

Chronic hyperglycemia is associated with damage and dysfuncion of different systems of organs, of which complications are most commonly seen in the nervous and cardiovascular system.(16) Diabetic patients sometimes have autonomic dysregulation, caused by neuropathy and damaged nerve endings. This change is seen foremostly on blood vessels, disabling adequate wall muscle tonus, as well as on the heart muscle where it reduces and sometimes disables physiological response to changes in preassure, volume and increased need during exercise.[17] A change in heart rate during exercise is used as a marker of preservation of the myocardial autonomic innervation, more precisely the decrease of heart rate in the first minute of resting after physical activity or pharmacological effort. Potential prognostic value of HRR as a marker for cardiac and all-cause mortality has been described in literature.[14] In our paper there was a tendency for the prognostic value of HRR to be statistically significant, therefore it can be hypothesized that the difference would have been significant had there been a larger number of patients included.

The next important parameter that showed a statistically significant difference between groups was the Duke score. Its prognosic value in events related to cardiological complications has been described in literature in detail and is considered today as an indispensable scoring system during stress testing.[18–20] including ST-segment depression, chest pain, and exercise duration. However, its usefulness for providing diagnostic estimates has yet to be determined. Methods and Results - A logistic regression model was used to predict significant (≥75% stenosis Our research showed that patients with silent ischemia during stress testing had a significantly lower Duke score values, which is related to a higher rate of cardiovascular mortality.[21] This correlates with our findings regarding to the occurence of MACE, which were significantly more common in patients with silent ischemia.

Conclusion

Patients with silent myocardial ischemia had a significantly higher risk of major adverse cardiac events in the long-term follow-up period compared to patients without silent ischemia. There was a statistically insignificant difference in the value of HRR between patients with and without silent ischemia. Studies with a larger number of patients are needed in order to determine the significance of HRR after stress testing in predicting adverse events in patients with diabetes and silent ischemia.

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Sažetak

Prognostički značaj oporavka srčane frekvence kod bolesnika sa dijabetesom melitusom i „nemom” ishemijom

Predrag Jančić[1], Emilija Jančić[1], Vojislav Giga,[1,2] Nikola Bošković[2], Marko Banović[1,2]
1Medicinski fakultet, Univerzitet u Beogradu, 2Klinika za kardiologiju, Univerzitetski Klinički centar Srbije

Uvod: *Oporavak srčane frekvence (OSF) nakon testa opterećenja predstavlja jedan od pokazatelja normalne vagalne aktivnosti koja je povezana sa rizikom od prevremene smrti. Stoga, treba ispitati prognostičku vrednost ovog parametra za moguće neželjene događaje, pogotovo kod bolesnika sa dijabetesom kod kojih je inervacija srca često oštećena.*
Metod: *U istraživanje je uključeno 112 bolesnika. Bolesnici su podeljeni na one sa nemom ishemijom miokarda i one bez nje. Praćena su četiri glavna neželjena događaja (MACE): revaskularizacija miokarda, popuštanje srca sa hospitalizacijom, infarkt miokarda i smrtni ishod. Medijana praćenja bolesnika je iznosila pet godina.*
Rezultati: *Bolesnici sa nemom ishemijom su imali značajno manji OSF u odnosu na bolesnike bez nje (22,8 ± 10,4 vs. 29,4 ± 13,8 otkucaja u minuti, p=0,031). Rizik od pojave MACE-a bio je značajno veći u grupi sa nemom ishemijom u odnosu na one bez nje (54,2% vs. 25%, p=0,006). Grupa bolesnika sa nemom ishemijom je imala 2,88 puta veći rizik od pojave MACE-a u dugoročnom period praćenja, u odnosu na grupu bolesnika bez nje (HR 2,88; 95%CI: 1,449-5,174; p=0,03). Grupa bolesnika sa sporim OSF je imala skoro 2 puta veći rizik od pojave MACE-a u dugoročnom period praćenja, u odnosu na grupu bolesnika sa normalnim OSF (HR 1.918; 95%CI: 0.939-3.916; p=0.074).*
Zaključak: *Bolesnici sa dijabetesom i nemom ishemijom miokarda imali su značajno veći rizik od pojave MACE u dugoročnom periodu praćenja u odnosu na bolesnike bez neme ishemije. Za utvrđivanje značaja OSF u predikciji neželjenih događaja kod bolesnika sa nemom ishemijom potrebne su studije sa većim brojem bolesnika.*

Ključne reči: *stres-ehokardiografski test, dijabetes melitus, ishemija miokarda*