



Prognostic value of heart rate variability in post-infarction patients

Prognostički značaj varijabilnosti srčane frekvencije kod bolesnika nakon infarkta miokarda

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Abstract

Background/Aim. Depressed heart rate variability (HRV) indicating autonomic disequilibrium and propensity to ventricular ectopy can be useful for risk stratification in patients following acute myocardial infarction (AIM). The aim of the study was to assess heart rate variability as a predictor of all-cause mortality in post-infarction patients. **Methods.** We analyzed the 24-hour electrocardiographic (ECG) recordings of 100 patients (80 males) during hospitalization for AIM. The mean age of patients was 56.99 ± 11.03 years. Time domain heart rate variability analysis was obtained from 8 to 13 days after index infarction by mean of a 24-hour ECG recording, and the calculated parameters were: standard deviation of all normal to normal RR intervals (SDNN), RRmax-RRmin (difference between the longest RR interval and the shortest RR interval), mean RR interval. We also analyzed ventricular premature complexes from the ECG data. The patients underwent clinical evaluation, laboratory tests and echocardiography. **Results.** Within a one-year follow-up period 11 patients experienced death, 10 of them because of cardiac reason and one because of stroke. There were significantly lower values of SDNN (60.55 ± 12.84 ms *vs* 98.38 ± 28.21 ms), RRmax-RRmin (454.36 ± 111.00 ms *vs* 600.99 ± 168.72 ms) and mean RR interval (695.82 ± 65.87 ms *vs* 840.07 ± 93.97 ms) in deceased patients than in the survivors, respectively ($p < 0.01$). The deceased patients were of higher mean age, with lower left ventricular ejection fraction (0.46 ± 0.05 *vs* 0.56 ± 0.06 in survivors), and more frequent clinical signs of heart failure and ventricular ectopic activity ($> 10\text{VPCs/h}$; $p < 0.01$). Multivariate Cox analysis showed that SDNN was a significant, independent predictor of all-cause mortality in post-infarction patients. The other independent predictors were clinical signs of heart failure – Killip class II and III and ventricular ectopic activity. **Conclusion.** Depressed HRV is an independent predictor of mortality in post-infarction patients and may provide useful additional prognostic information in non-invasive risk stratification of these patients.

Key words:

myocardial infarction; heart rate; arrhythmias, cardiac; mortality; risk factors; predictive value of tests.

Apstrakt

Uvod/Cilj. Smanjena varijabilnost srčane frekvencije kao pokazatelj neuravnoteženosti autonomnog nervnog sistema i sklonosti ka ventrikularnim ekstrasistolama može biti korisna za stratifikaciju rizika kod bolesnika nakon akutnog infarkta miokarda. Cilj studije bio je da se ispita prognostički značaj varijabilnosti srčane frekvencije za ukupni mortalitet kod ovih bolesnika. **Metode.** Analizirali smo 24-časovno Holter elektrokardiografsko praćenje 100 bolesnika za vreme hospitalizacije zbog akutnog infarkta miokarda. Prosečna starost bolesnika bila je $56,99 \pm 11,03$ godine, od kojih je bilo 80 muškaraca. *Time domain* analiza varijabilnosti srčane frekvencije određivana je od 8. do 13. dana od nastanka akutnog infarkta miokarda, uz upotrebu 24-časovnog Holter posmatranja, a izračunavani parametri bili su: standardna devijacija svih normalnih RR intervala (SDNN), RRmax-RRmin (razlika između najdužeg RR intervala i najkraćeg RR intervala) i prosečni RR interval. Iz Holter posmatranja, takođe, analizirani su ventrikularni poremećaji ritma. Kod bolesnika je obavljeno i kliničko praćenje, laboratorijski testovi i ehokardiografsko ispitivanje. **Rezultati.** Tokom perioda praćenja od godinu dana, 11 bolesnika je umrlo, od čega 10 zbog kardijalnog uzroka, a jedan usled cerebro-vaskularnog inzulta. Registrovane su značajno niže vrednosti SDNN ($60,55 \pm 12,84$ ms *vs* $98,38 \pm 28,21$ ms), RRmax-RRmin ($454,36 \pm 111,00$ ms *vs* $600,99 \pm 168,72$ ms) i prosečnog RR intervala ($695,82 \pm 65,87$ ms *vs* $840,07 \pm 93,97$ ms) kod umrlih u odnosu na preživeli ($p < 0.01$). Preminuli bolesnici bili su stariji, sa nižom ejekcijskom frakcijom leve komore ($0,46 \pm 0,05$ *vs* $0,56 \pm 0,06$), češćim kliničkim znacima srčane insuficijencije i ventrikularnim poremećajima ritma ($> 10\text{VES/h}$; $p < 0,01$). Multivarijantna Cox analiza pokazala je da je SDNN značajan, nezavisan prediktor za ukupni mortalitet kod bolesnika nakon infarkta miokarda. Drugi nezavisni prognostički faktori bili su klinički znaci srčane insuficijencije – Killip klasa II i III i učestale ventrikularne ekstrasistole. **Zaključak.** Smanjena varijabilnost srčane frekvencije je nezavisan prediktor mortaliteta kod bolesnika nakon infarkta miokarda i može pružiti korisne dodatne prognostičke informacije u neinvazivnoj stratifikaciji rizika kod ovih bolesnika.

Ključne reči:

infarkt miokarda; srce, frekvencija; aritmija; mortalitet; faktori rizika; testovi, prognostička vrednost.

Introduction

The process of risk stratification following acute myocardial infarction (AMI) occurs in three stages: initial presentation, hospital course and assessment at hospital discharge¹. It requires tests which can assess myocardial function, residual ischemia and propensity for ventricular arrhythmias. The most important determinant for mortality is left ventricular function, and left ventricular ejection fraction (LVEF) below 40% is a strong predictor of death in post-infarction patients². Susceptibility to serious arrhythmias is reflected in ventricular ectopic activity, and other indicators of electrical instability such as depressed heart rate variability (HRV) or baroreflex sensitivity and an abnormal signal-averaged electrocardiogram^{3,4}. All of these can identify patients at increased risk of death. Depressed HRV in post-MI patients may reflect a decrease in vagal activity directed to the heart, which leads to prevalence of sympathetic mechanisms and to cardiac electrical instability.

The association of higher risk of post-infarction mortality with reduced HRV was first shown by Wolf et al.⁵ in 1977. The variation of heart rate may be evaluated by a number of methods. The simplest to perform is the time domain measure of the standard deviation of all normal RR intervals (SDNN), which is most frequently used. More complicated are various spectral methods for the analysis of the tachogram – frequency domain methods. According to Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology, SDNN is recommended as a measure of HRV in post-infarction patients; SDNN is calculated over a 24-hour period from a continuous electrocardiographic (ECG) recording in patients before discharge from the hospital⁶. SDNN < 70 ms was used in several independent studies as a cutoff value defining normal and depressed HRV and a powerful predictor of mortality and arrhythmic complications in patients after AMI^{2,4}. The predictive value of HRV is independent of other factors established for post-infarction risk stratification, such as depressed LVEF, increased ventricular ectopic activity, and the presence of ventricular late potentials. In the era of modern treatment strategies that have modifying role in prognosis of post-MI patients, such as treatment with beta blockers, ACE inhibitors, revascularization and implantable cardioverter defibrillators (ICD), the prognostic significance of HRV has been challenged.

The aim of this study was to assess prognostic value of HRV in post-MI patients during the follow-up of one year.

Methods

The study was observational and prospective and included 110 patients with AMI who were admitted in the Coronary Care Unit of Clinical Center of Montenegro in Podgorica. Entry criteria were the diagnosis of first AMI with ST elevation, the age of 80 years or younger, and sinus rhythm. Exclusion criteria were atrial fibrillation or abnormal sinus node function, valvular disease or cardiomyopathy, and any other disease limiting survival. The study was approved

by the Ethics Committee of the institution. Since the data obtained were non-invasive and did not exceed usual clinical management of the patients, the local Ethics Committee decided that signed informed consent was not needed. However, we did obtain oral informed consent.

Medical history, physical examination and laboratory findings were undertaken for all the patients. LVEF was measured within the two weeks of the index infarction by two-dimensional echocardiography. HRV and arrhythmia analysis (frequent ventricular premature complexes-VPCs > 10 VPCs/hour, VPC couplets and non-sustained ventricular tachycardia – NSVT) were measured by Holter-monitoring (24-hour ECG recording). Recordings were obtained from 8 to 13 days after an index infarction and contained at least 19 hours of analyzable ECG data including the whole night coverage. Biosensor Holter recorders were used. Tapes were analyzed for ventricular arrhythmias and HRV at the Holter laboratory of the Clinical Center of Montenegro by the published methods (a software package of Microsoft Corporation, after visual and manual editing of RR intervals and QRS complexes). The measure of HRV chosen for the primary analysis was SDNN calculated from 24-hour ECG recording, which represents measure of the global HRV. We also calculated simple time domain measures of HRV: RRmax-RRmin (difference between the longest RR interval – RRmax and the shortest RR interval – RRmin) and the mean RR interval (mean of all normal RR intervals). All the patients took their usual medications on the day of ECG recording.

The patients were followed-up for one year with visits every 6 months. All clinical events during the follow-up period were recorded and for patients who died we asked for the cause of death. The end-point of the study was all-cause mortality (death from any cause) and sudden cardiac death (SCD), which occurring instantaneous to 1 hour after the onset of a change in clinical status. In seven patients 24-hour ECG recording was not technically good for interpretation. We lost contact with three patients during the follow-up of one year. At the end of the study we had data of 100 patients for statistical analysis.

The arithmetic mean and standard deviation ($\bar{x} \pm SD$) were calculated for continuous variables. χ^2 and Independent Sample *t*-test were used to evaluate associations between the categorical and continuous variables. Statistical analysis was performed by using the statistical package SPSS 15.0 for Windows and data base in Microsoft Excel package. For identification of prognostic factors-predictors we used multivariate Cox analysis. A two-tailed *p* value of less than 0.05 was accepted as significant.

Results

We observed 110 patients, but at the end of the study we had data of 100 patients for statistical analysis. The mean age of patients was 56.99 ± 11.03 years, between them 80 were men and 20 women, mean BMI was 26.72 ± 3.44 kg/m². Anterior localization of AMI was diagnosed in 44% of the patients and inferior localization of AMI in 56% of the

patients. Physical examination found that 68% of the patients had Killip I class, 28% of them Killip II class and 4% of the patients had Killip III class during the stay in the Coronary Care Unit; mean LVEF was 0.54 ± 0.07 . Analysis of HRV showed that mean SDNN was 94.22 ± 29.42 ms; 23% of the patients had SDNN < 70 ms; mean RR interval was 824.20 ± 101.71 ms and mean RRmax-RRmin was 584.86 ± 169.33 ms. Analysis of ventricular ectopic activity found that 16% of the patients had > 10 VPCs/hour. During a follow-up period of one year 11 patients died, 10 of them because of cardiac reason and one died of stroke. Among the patients who had cardiac death, 6 patients had SCD and 4 had worsening of congestive heart failure as a cause of death. Three patients died in the first 30 days after AMI, two patients had SCD and the third patient died because of congestive heart failure. Demographic and clinical characteristics of the patients are shown in Table 1. There was no difference in revascularization strategy between the patients who survived and the deceased patients, 51% of those treated with thrombolysis and

no one with primary PCI ($p > 0.05$), but treatment with beta blockers was more frequently used in patients who survived ($p < 0.05$), without any differences in other medical therapy.

Analysis of HRV showed significantly lower values of SDNN (60.55 ± 12.84 ms vs 98.38 ± 28.21 ms), RRmax-RRmin (454.36 ± 111.00 ms vs 600.99 ± 168.72 ms) and the mean RR interval, (695.82 ± 65.87 ms vs 840.07 ± 93.97 ms) in the patients who died than in the survivors ($p < 0.01$) (Table 2).

The study findings showed depressed HRV – SDNN < 70 ms in 23 of the patients, and it was more frequent in the patients who died (9/11), than in those who survived (14/89; $p < 0.01$).

Ventricular ectopic activity, the number of ventricular premature complexes (VPCs) > 10/hour was more frequent in the patients who died than in the survivors ($p < 0.01$) (Table 3). There was no significant difference in the number of couplets and episodes of NSVT during Holter monitoring in patients who died compared to patients who survived ($p > 0.05$).

Table 1

Demographic and clinical characteristics of the study population

Characteristics of patients	Survived (n = 89)	Dead (n = 11)	<i>p</i>
Age (years), $\bar{x} \pm SD$	58.78 ± 10.82	62.83 ± 7.35	< 0.01
Male/Female (n)	72/17	8/3	> 0.05
BMI (kg/m^2), $\bar{x} \pm SD$	26.62 ± 3.34	27.24 ± 4.21	> 0.05
Smoker (n)	63	7	> 0.05
Hypertension (n)	44	6	> 0.05
Hyperlipidemia (n)	27	3	> 0.05
Diabetes mellitus (n)	14	2	> 0.05
Heart rate at admission (b.p.m.), $\bar{x} \pm SD$	82.78 ± 21.26	79.82 ± 28.81	> 0.05
Systolic blood pressure (mmHg), $\bar{x} \pm SD$	138 ± 22	142 ± 24	> 0.05
Diastolic blood pressure (mmHg), $\bar{x} \pm SD$	89 ± 14	93 ± 12	> 0.05
Hemoglobin (g/l), $\bar{x} \pm SD$	141 ± 10	136 ± 12	> 0.05
Glucose (mmol/L), $\bar{x} \pm SD$	7.42 ± 1.25	7.15 ± 1.43	> 0.05
Creatinine ($\mu\text{mol/L}$), $\bar{x} \pm SD$	82.38 ± 29.24	85.14 ± 31.18	> 0.05
Total cholesterol (mmol/L), $\bar{x} \pm SD$	6.21 ± 1.33	6.06 ± 1.42	> 0.05
LDL- cholesterol (mmol/L), $\bar{x} \pm SD$	4.22 ± 1.24	3.98 ± 1.45	> 0.05
HDL- cholesterol (mmol/L), $\bar{x} \pm SD$	1.14 ± 0.21	1.20 ± 0.31	> 0.05
Triglycerides (mmol/L), $\bar{x} \pm SD$	2.01 ± 1.12	1.93 ± 1.23	> 0.05
Sodium (mmol/L), $\bar{x} \pm SD$	138.11 ± 2.24	139.39 ± 2.95	> 0.05
Potassium (mmol/L), $\bar{x} \pm SD$	4.32 ± 0.43	4.16 ± 0.36	> 0.05
Creatin kinase Mb peak (IU/L), $\bar{x} \pm SD$	100.44 ± 83.40	118.39 ± 72.37	> 0.05
Killip class I / II / III (n)	67 / 20 / 2	1 / 8 / 2	< 0.01
Left ventricular ejection fraction (%), $\bar{x} \pm SD$	0.56 ± 0.06	0.46 ± 0.05	< 0.01

BMI – body mass index; LDL – low density lipoprotein; HDL – high density lipoprotein.

Table 2

Heart rate variability and mortality

Parameter	Survived $\bar{x} \pm SD$	Dead $\bar{x} \pm SD$	<i>p</i>
SDNN (ms)	98.38 ± 28.21	60.55 ± 12.84	< 0.001
Mean RR interval (ms)	840.07 ± 93.97	695.82 ± 65.87	< 0.001
RRmax-RRmin (ms)	600.99 ± 168.72	454.36 ± 111.00	0.006

SDNN – standard deviation of all normal RR intervals.

Table 3

Ventricular ectopic activity (> 10 VPCs/hour) and mortality

> 10 VPCs / h	Survived	Dead	χ^2	<i>p</i>
Yes	11	5	7.978	0.009
No	78	6		

VPC – ventricular premature complex.

Multivariate Cox analysis showed that SDNN was a significant, independent predictor of all-cause mortality and cardiac mortality in post-infarction patients ($p < 0.01$), but SDNN was not an independent predictor of SCD ($p > 0.05$). Also the independent predictors of all-cause mortality and cardiac mortality were the clinical signs of heart failure – Killip class II and III, ($p < 0.01$) and a ventricular ectopic activity (number of VPCs > 10 /hour; $p < 0.05$) (Table 4). The independent predictors of SCD were the mean heart rate (RR 1.14; CI 1.04–1.26, $p = 0.0053$) and the ventricular ectopic activity (the number of VPCs > 10 /hour) at Holter monitoring (RR 17.84; CI 2.03–156.51, $p = 0.0093$); the higher mean heart rate was associated with the higher risk for SCD.

and heart rate. Our study showed that the mean heart rate at Holter monitoring was an independent predictor of SCD additive to frequent ventricular ectopic activity (> 10 VPCs/hour).

The results of GISSI-2 study demonstrated that SDNN < 70 ms was an independent predictor of cardiac mortality in patients after myocardial infarction¹¹. The findings of ATRAMI study showed that low baroreflex sensitivity and low SDNN contributed to high risk of cardiac mortality in post-MI patients and that an altered cardiac substrate, identified by depressed LVEF and by the presence of frequent VPCs, was not the sole significant predictor of post-infarction cardiac mortality⁴. These findings pointed to the critical role of an altered autonomic balance that resulted in a

Table 4

Cox analysis of the predictors of all-cause mortality

Variable	B	S.E.	Wald	df	<i>p</i>	<i>r</i>	EXP (B) RR	95% CI for EXP(B)
Killip class	2.31	0.83	7.79	1	0.0052	0.25	10.11	1.99–51.27
SDNN	-0.12	0.03	13.57	1	0.0002	-0.36	0.89	0.84–0.95
> 10 VPCs/h	1.78	0.72	6.10	1	0.0135	0.21	5.90	1.44–24.16

SDNN – standard deviation of all normal RR interval; VPC – ventricular premature complex.

Discussion

Prediction of fatal events in patients following AMI is very difficult, especially non-invasive risk stratification. The assessment of left ventricular function, use of signal-averaged electrocardiography and Holter monitoring were shown to be predictive for future mortality and arrhythmic events in patients after AMI. There is a clear progressive increase in mortality, especially as the LVEF falls $< 40\%$ ². Multivariate analysis showed that VPCs frequency and complexity are also an independent risk factor for total cardiac mortality and SCD^{7–9}.

Our study provides evidence that, beside clinical signs of heart failure and frequent VPCs, HRV has independent prognostic value in post-MI patients. We demonstrated that SDNN value was independently inversely associated with the risk of all-cause mortality after an acute myocardial infarction with ST segment elevation, but not with the risk of SCD. We showed that increased mean heart rate and frequent ventricular ectopy on post-infarction Holter recording independently predicted increased risk of SCD. The knowledge of a patient's autonomic status improves risk stratification over and beyond that obtained from the established clinical predictors such as clinical signs of heart failure, LVEF, and ventricular arrhythmias. It has become clear that autonomic nervous system is very important in the pathogenesis of ventricular arrhythmia and death.

Kleiger et al.¹⁰ pointed that HRV had the strongest univariate correlation with mortality in 808 post-infarction patients. Patients with reduced HRV had higher mortality, independent of the LVEF. Patients with a SDNN < 50 ms had a relative risk of all-cause mortality of 2.8. These studies showed that HRV was an independent predictor of death additive to other post-infarction risk variables, such as LVEF

relatively high sympathetic activity and a low vagal activity as showed by low values of baroreflex sensitivity and SDNN.

A meta-analysis of 51 trials included 3,489 post-infarction patients with an overall mortality of 125/577 (21.7%) in patients with SDNN < 70 ms compared to 235/2912 (8.1%) in patients with SDNN > 70 ms. The meta-analysis demonstrated that, after a myocardial infarction, patients with SDNN < 70 ms had almost four times more chance to die in the next 3 years than those with SDNN > 70 ms^{12, 13}. The results of a CARISMA study suggest that fatal or near-fatal arrhythmias can be predicted by many risk stratification methods, especially by heart rate variability, in patients with reduced LVEF after AMI¹⁴.

Our findings showed significantly lower SDNN in patients who died than in those who survived, mortality was higher in patients with SDNN < 70 ms, and depressed HRV was an independent predictor of all-cause mortality and cardiac mortality in post-MI patients in addition to the clinical signs of heart failure and frequent VPCs. Treatment with beta blockers was more frequently used in patients who survived, without a difference in revascularization strategy and other medical therapy. This observation might explain higher SDNN and better prognosis in patients treated with beta blockers. These drugs possibly can increase HRV. The decrease in sympathetic activity was noticed in post-infarction patients using metoprolol¹⁵ and in patients with heart failure using acebutolol¹⁶. Thus, beta blockers are able to restore the sympathetic–parasympathetic balance in cardiovascular disease. The deceased patients in our study were of higher mean age and with lower left ventricular ejection fraction, too.

Risk stratification of post-infarction patients is important since the preventive therapy with ICD is effective in re-

ducing mortality. The guidelines for primary prevention with ICD in post-infarction patients basically use LVEF for risk stratification (at least 40 days after AMI)^{17,18}. However, many deaths occur in low-risk patients with normal LVEF who do not fulfill criteria for ICD implantation, and some patients with an ICD do not appear to gain benefit from the device^{19–21}. There is no ideal particular test for risk stratification in patients following AMI. There is a need for combination of tests^{22–26}. The findings of some studies showed combination of LVEF $\leq 40\%$ + reduced HRV + frequent VPCs on Holter monitoring had positive predictive value of 50%⁹. For example in a DINAMIT study, designed to assess the impact of ICD implantation on top of optimal medical therapy (OMT) versus OMT alone on all-cause mortality in high-risk patients within 40 days after AMI, the inclusion criteria were the occurrence of AMI 6–40 days prior to enrollment, LVEF $\leq 35\%$, SDNN ≤ 70 ms and the mean RR interval ≤ 750 ms (the last three criteria were used for stratification of high-risk patients)²⁷. A review of the literature suggested staged combination of tests, with Intracardiac Electrophysiology Study (EPS) last, which allowed 91.8% of patients to be stratified as either high or low risk^{24,28}. Further investigations will be needed to determine the most useful predictive combination of tests for risk stratification in post-infarction patients.

The limitations of our study include a small number of patients and a small number of events in each group and therefore study could be underpowered to detect long-term mortality difference.

Conclusion

This study shows that depressed heart rate variability is an independent predictor of mortality in post-infarction patients additive to clinical signs of heart failure and ventricular ectopic activity and may provide useful additional prognostic information in non-invasive risk stratification. These findings suggest that in post myocardial infarction patients reduction in vagal activity, which is almost always accompanied by a concomitant increase in sympathetic activity, is associated with higher risk for death. Heart rate variability is simple, non invasive and relatively not expensive to obtain.

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Conflicts of interest

The authors declare no conflict of interest.

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