Prognostic value of decreased heart rate variability in long-term follow-up in patients with acute myocardial infarction treated with thrombolysis

Anna Olasińska-Wiśniewska[1], Tatiana Mularek-Kubzdela[1], Wojciech Seniuk[1], Piotr Bręborowicz[1], Hanna Wachowiak-Baszyńska[1], Jadwiga Kowal[1], Marek Grygier[1], Małgorzata Popiel[1], Włodzimierz Skorupski[1], Marcin Misterski[2], Aleksander Araszkiewicz[1], Romuald Ochotny[1], Stefan Grajek[1]

[1]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland
[2]Department of Cardiac Surgery, Poznan University of Medical Sciences, Poznan, Poland

Submitted: 18 August 2007
Accepted: 28 January 2008

Arch Med Sci 2009; 5, 1: 97-102

Corresponding author:
Anna Olasińska-Wiśniewska
1st Department of Cardiology
Długa Street 1/2
61-848 Poznań, Poland
Phone: +48 61 8549146
Fax: +48 61 8549094
E-mail:
anna.olasinska@poczta.onet.pl

Abstract

Introduction: In previous decades, the analysis of heart rate variability (HRV) provided a non-invasive method of assessing autonomic influence for cardiovascular risk stratification. The aim of this study was to determine whether HRV analysis can still perform a similar function in the present day.
Material and methods: The study group consisted of 113 patients with acute myocardial infarction (AMI) treated with thrombolysis. In all patients echocardiography on the 10th day after myocardial infarction and 24-h Holter electrocardiographic recordings on the 12th day after myocardial infarction were performed. Five time domain measures were calculated from the time series of normal N-N intervals: SDNN, SDANN index, SDNN index, rMSSD and pNN50. The end points in follow-up were: death, non-fatal myocardial infarction (AMI) and unstable angina pectoris requiring hospitalization (API). The study group was divided into two subgroups on the basis of SDNN value and both groups were analysed.
Results: At follow-up (mean 65 months, range 36 to 96 months) we observed clinical events in 44 patients, including 17 deaths, 8 cases of AMI and 20 cases of API requiring hospitalization. In the multivariate analysis SDNN ≤ 70 ms as well as left ventricle ejection fraction < 30% were independent predictors of death.
Conclusions: SDNN ≤ 70 ms remains a significant predictor of death in patients with MI treated with thrombolysis.

Key words: heart rate variability, acute myocardial infarction.

Introduction

Autonomic system imbalance plays an important role in several cardiological and non-cardiological diseases. Disturbances of the autonomic nervous system and its imbalance, consisting of either increased sympathetic or reduced vagal activity, may result in ventricular tachyarrhythmias and sudden cardiac death [1-4]. Heart rate variability (HRV) has been shown to be depressed in many cardiological disorders, including coronary heart disease, heart failure and some congenital heart diseases [5-11], and has

also been used for the screening of patients with obstructive sleep apnoea [12]. The usefulness of HRV in differentiating vasovagal patients from others suffering from syncope has also been shown [13].

The analysis of HRV has provided a non-invasive method of autonomic influence assessment and cardiovascular risk stratification. Of all Holter variables measured, HRV had the strongest univariate correlation with mortality. Depressed HRV after acute myocardial infarction (AMI) may reflect a decrease in vagal activity in the heart, which leads to the dominance of sympathetic mechanisms and cardiac electrical instability. Casolo *et al.* reported that for patients with congestive heart failure the best prediction for risk stratification was provided by: ultra-low frequency power, very low frequency power, standard deviation of all normal RR intervals in the entire 24-h ECG recording (SDNN), standard deviation of the average normal RR intervals for all 5-min segments of a 24-h ECG recording (SDANNI) and mean of the standard deviations of all normal RR intervals for all 5-min segments of a 24-h ECG recording (SDNNI) [14]. According to Bigger *et al.*, not only long-term HRV (24-h values) but also short-term HRV (calculated from 2-15 min of normal RR interval data) measured in patients after MI had predictive value for 1-year total cardiac mortality [15, 16].

However, few previous studies have been followed up over a long term. The aim of this study was to determine the long-term predictive role of HRV in the cardiovascular risk stratification for patients with acute myocardial infarction treated with thrombolysis. Most previous studies which estimated HRV value were performed in the late 1980s. A major potential difference between earlier studies and our study lies in the fact that all our patients were treated with early thrombolysis and such medication as angiotensin-converting enzyme inhibitors and β-blockers are much more widely used. A further aim of the study was to determine the correlation between HRV and adverse prognosis in a population of patients with AMI treated with thrombolysis and additional medication administered according to state-of-the-art current guidelines, in long-term follow-up. We intended to establish the HRV value which predicts adverse prognosis in this population.

Material and methods

Patients

One hundred and thirteen consecutive patients (89 male and 24 female, aged 34 to 81, mean 57 ±10.8) admitted to our department for AMI and treated with thrombolysis (streptokinase or tissue plasminogen activator – tPA) were enrolled in the study between 1994 and 1996. Mean follow-up time was 65 months (range 36 to 96 months). Acute myocardial infarction was defined by the typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB, with ischaemic symptoms and/or development of pathological Q waves in the ECG and/or ECG changes indicative of ischaemia. For each patient the medical history was collected and a physical examination was performed. Exclusion criteria were atrial fibrillation or implanted pacemakers.

Assessment of left ventricle ejection fraction

Echocardiography was performed in each patient (on the 10th day) by a cardiologist.

Analysis of 24-h electrocardiographic recordings

24-h Holter electrocardiographic recording was performed on all patients on the 12th day after myocardial infarction. Holter tapes were reanalyzed using a high-performance digital computer program for identifying each QRS. After the computer had automatically detected and labelled each QRS, the data file was reviewed and edited by a cardiologist. After completing the editing process, another computer program computed the average N-N interval for all normal cycles, the standard deviation of N-N intervals around this average and other summary measures of HR and HR variability. From the time series of normal N-N intervals, five time domain measures were calculated: SDNN (standard deviation of all normal RR intervals in the entire 24-h ECG recording); SDANN index (standard deviation of the average normal RR intervals for all 5-min segments of a 24-h ECG recording); SDNN index (mean of the standard deviations of all normal RR intervals for all 5-min segments of a 24-h ECG recording); rMSSD (root-mean-square successive difference – the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-h ECG recording); and pNN50 (percentage of differences between adjacent normal RR intervals that are > 50 ms computed over the entire 24-h ECG recording).

Follow-up

Patients were followed up with visits, phone calls and questionnaires. Mean follow-up time was 65 months (range, 36 to 96 months). The end points were: death, non-fatal acute myocardial infarction, or unstable angina pectoris requiring hospitalization. We did not distinguish between cardiac death and non-cardiac death.

Statistical analysis

Data are reported as mean ± standard deviation (x ± SD). The data analyses were performed using

CSS STATISTICA for Windows, release 7.1. Comparisons between groups were performed by unpaired *t*-test and Fisher's exact test as indicated. Statistical significance was considered when $p < 0.05$. The association of SDNN with prognosis was studied by discrimination linear test analysis.

The study was approved by the local ethics committee.

Results

The baseline clinical characteristics of the study population are shown in Table I. During the hospital stay, 76 (67.2%) patients were treated with β-blockers and 52 (46%) with angiotensin-converting enzyme (ACE) inhibitors.

Based on the presence or absence of clinical events the patients were divided into two groups. The Event Group consisted of 44 patients who experienced a clinical event [17 deaths (calculated mortality rate was 15%), 9 cases of non-fatal AMI and 21 cases of unstable angina pectoris (API) requiring hospitalization], with the remaining 69 patients (without clinical events) placed in the Non-Event Group. Table II shows the mean values of five time-domain indices of HRV (SDNN, SDANNI, SDNNI, rMSSD and pNN50). The mean SDNN, SDNNI and SDANNI values in the Event Group were lower than in the Non-Event Group, but the difference was not significant. Table III presents the general and clinical characteristics of both groups.

The patients were also divided into two further groups according to their SDNN value: A, with SDNN ≤ 70 ms (27 patients); and B, with SDNN > 70 ms (86 patients). The clinical characteristics of these groups are shown in Table IV.

The relationship between clinical end points and the SDNN cut-off value is shown in Table V. There was a correlation between clinical events and SDNN value ≤ 70 ms.

In multivariate analysis the following variables were considered in the model: SDNN ≤ 70 ms ($p = 0.005$), LVEF < 30% ($p = 0.044$), age ($p = 0.3$), CKMB ($p = 0.3$) and arterial hypertension ($p = 0.8$). Only SDNN ≤ 70 ms and LVEF < 30% were independent predictors of death.

Discussion

Determining the prognostic value of HRV for identification of high-risk patients has been the objective of many experimental and clinical studies in the last few decades [1, 2, 4]. Nevertheless, the position of HRV in modern cardiology is still uncertain. Currently, according to the ACC/AHA Guidelines for Ambulatory Electrocardiography [17], only patients with left ventricle dysfunction after myocardial infarction, without symptoms of arrhythmia, may benefit from HRV measurements for risk assessment.

More recent studies have analysed the population of patients given newer treatment

Table I. Demographic and clinical characteristics

Demographic and clinical characteristics	Number (percentage of patients)
Male	89 (78.7%)
Age	mean 57 (range 34-81)
History of:	
• angina pectoris	47 (41.6%)
• myocardial infarction	20 (17.7%)
• congestive heart failure	3 (2.6%)
Arterial hypertension	42 (37.2%)
Diabetes	14 (12.4%)
Anterior wall myocardial infarction	43 (38%)

Table II. The mean values of five time-domain indices of HRV in the Event and the Non-Event groups

	Event group [ms]	Non-Event group [ms]	*p*
SDDN	90.6 ±32.9	99.3 ±33.7	0.2
SDNNI	42.3 ±18.9	44.1 ±14.1	0.6
SDANNI	78.4 ±28.8	87.2 ±34.4	0.2
rMSSD	27.7 ±15.2	26.1 ±12.2	0.5
pNN50	7.6 ±9.4	6.5 ±9.8	0.6

Table III. General and clinical characteristics of the Event Group and the Non-Event Group

	Event group ($n = 44$)	Non-Event group ($n = 69$)	*p*
Age	58.9 ±11.2	56.6 ±10.6	0.3
Male	32 (72.7%)	57 (82.6%)	0.2
CK	2590.2 ±2552.7	2757.8 ±2092.9	0.7
Anterior wall myocardial infarction	19 (43.2%)	35 (50.7%)	0.4
β-blockers	29 (65.9%)	47 (68.1%)	0.8
ACEI	20 (45.5%)	32 (46.4%)	1.0
History of myocardial infarction	11 (25.0%)	9 (13.0%)	0.1
History of angina pectoris	27 (61.4%)	20 (29.0%)	0.0009
Hypertension	21 (47.7%)	21 (30.4%)	0.075
Diabetes	6 (13.6%)	8 (11.6%)	0.8
Smokers	28 (63.6%)	36 (52.2%)	0.2
Hypercholesterolaemia	15 (34.1%)	18 (26.1%)	0.4
Family history	22 (50%)	31 (44.9%)	0.7

vs. the populations involved in earlier studies on HRV. New methods of treatment for acute coronary syndromes – early thrombolysis, acute coronary interventions and medications such as ACEI and β-blockers – have recently been introduced. In our study 67% of patients were given β-blockers and in the Ortak *et al.* study [18] (2005) β-blockers were administered in 90% of patients. However, in earlier studies, such as the Kleiger *et al.* study [1], the Lanza *et al.* study [19], and the ATRAMI study [3], β-blockers were used in 32, 34 and 20% of patients, respectively. Also, thrombolysis and/or acute coronary interventions are currently introduced in a higher percentage of patients – 42% of patients were treated in the Lanza *et al.* study [19], 63% of patients in the ATRAMI study [3], and all patients in the Ortak *et al.* [18] and our study. Some authors [18, 20] have suggested that this progress in therapy could influence the major potential difference between earlier and more recent studies on the value of HRV as post-MI risk stratification [18, 20]. The standard use of thrombolytic treatment or urgent coronary revascularization has improved outcome in patients with acute myocardial infarction. The risk of developing malignant arrhythmia in patients within one year of myocardial infarction is less than 5% [4, 21], much lower than it was in the study of Kleiger *et al.* [1], who observed a 15.7% mortality rate during 31 months' follow-up in the early 1980s. Thus, early results suggesting the useful position of HRV should be re-analysed to assess its present significance.

Table IV. Differences in clinical characteristics according to SDNN value

	Group A SDNN ≤ 70 ms (27 patients) *n* (%)	Group B SDNN > 70 ms (86 patients) *n* (%)	*p*
Age	63.3	56	0.009
Male	21 (77.8%)	68 (79.1%)	1
Angina pectoris	15 (55.6%)	32 (37.2%)	0.1
Arterial hypertension	15 (55.6%)	27 (31.4%)	0.04
Diabetes	5 (18.5%)	9 (10.5%)	0.3
Hypercholesterolaemia	7 (25.9%)	26 (30.2%)	0.8
History of myocardial infarction	6 (22.2%)	14 (16.3%)	0.6
Anterior wall myocardial infarction	16 (59.3%)	38 (44.2%)	0.2
Ejection fraction	45.90%	52.50%	0.02
CKMB	259	190	0.05
In-hospital β-blocker	16 (59.3%)	60 (69.8%)	0.3

Table V. Clinical end points – association with the SDNN value

	Group A SDNN ≤ 70 ms (27 patients) *n* (%)	Group B SDNN > 70 ms (86 patients) *n* (%)	*p*
All clinical events	16 (59.2%)	28 (32.5%)	0.02
Deaths	9 (33.3%)	8 (9.3%)	0.0048
Myocardial infarction	4 (14.8%)	5 (5.8%)	0.2
Unstable angina pectoris requiring hospitalization	5 (18.5%)	16 (18.6%)	1.0

The Kleiger *et al.* [1] study demonstrated that of all Holter variables measured, HRV had the strongest correlation with mortality, independently of other risk factors, which were LVEF, frequency of ventricular extrasystoles, and non-sustained ventricular tachycardia (NSVT). Mean follow-up in Kleiger's group was 31 months. The relative risk of mortality was 5.3 times higher in the group with HR variability of less than 50 ms than in the group with HR variability of more than 100 ms. Our intention was to find an accurate HRV value, essential for stratification and clinical use, and to assess the usefulness of severely reduced HRV. The follow-up of our group was 65 months on average and during 96 months there was a 15% mortality rate, which is much lower than in Kleiger's study (15.7% mortality rate during 31 months' follow-up), possibly due to more intensive treatment with the use of early thrombolysis, β-blockers and ACE inhibitors. We analysed the relation between time domain indices of HRV and events occurrence. Our Event Group and Non-Event Group did not differ significantly in mean HRV values, but we observed higher values of SDNN in the Non-Event Group. Since time domain measures of HRV vary greatly in the population, including the population of patients after myocardial infarction, the value of standard deviation was relatively large. Thus, the analysis of the data from our study population and 24-h Holter electrocardiographic recordings impelled us to estimate the SDNN cut-off value and to divide patients into two groups based on the HRV cut-off value of 70 ms. The same value was used in the large, multicentre, prospective ATRAMI study [3]; however, in other studies different cut-off values were also found to be predictive: 50, 55, and 100 ms [1, 7, 19, 22, 23]. In the ATRAMI trial [3] the concomitant use of HRV and BRS (baroreflex sensitivity) for post-MI risk stratification showed that values of SDNN < 70 ms or BRS < 3.0 ms/mm Hg were both independent predictors of cardiac mortality. Our comparison of clinical findings in the two groups revealed that patients with lower SDNN values were older and had lower ejection fraction and higher CKMB levels. Concomitant arterial hypertension was higher in this group. We also observed slightly higher

incidence of angina pectoris (55.6 vs. 37.2%), diabetes (18.5 vs. 10.5%), history of myocardial infarction (22.2 vs. 16.3%) and anterior localisation of myocardial infarction (59.3 vs. 44.2%) in patients with lower SDNN values. These differences did not reach statistical significance, but may suggest that the subgroup with SDNN ≤ 70 ms had more risk factors and was a higher risk group. In follow-up this group presented higher mortality and this observation confirms our data. SDNN ≤ 70 ms appeared to be an independent predictor of death in multivariate analysis.

Many studies also examined the contribution of low LVEF and low HRV. In the ATRAMI study, survival of patients with LVEF below 35% was affected by low values of the autonomic markers. This was particularly evident with a low BRS value, which increased the 2-year mortality from 8 to 18%, but for SDNN the increase in mortality (from 9 to 13%) did not reach statistical significance. In the study by Kleiger *et al.* [1] EF < 30% appeared to be somewhat more significant in predicting mortality than SDNN in the multivariate analysis, while in the study by Farrel *et al.* [4] EF < 40% was excluded from the multivariate model. Lanza *et al.* [19] revealed that HRVs were not independent predictors of cardiac death in multivariate analysis, although a low frequency/high frequency ratio < 1.05 was of borderline statistical significance for sudden death.

In our study, in the multivariate analysis SDNN ≤ 70 ms as well as LVEF < 30% were independent predictors of death. We did not differentiate between cardiac death and non-cardiac death. Some authors support the opinion that the relative risk of several frequency and time domain indices were very consistent independently of the type of death taken as the end point, which may suggest that the prognostic power of HRV is unaffected by the mode of death [1, 23].

In the study by Camm *et al.* [24] patients with low HRV had significantly higher 1-year mortality after AMI than those with high HRV, despite nearly identical LVEF. Balanescou *et al.* [22] confirmed the prognostic significance of HRV indices expressing either a low vagal output (i.e. rMSSD < 20 ms), high sympathetic tone (i.e. LF/HF > 2) or low total autonomic activity (i.e. SDNN < 50 ms), independent from LVEF and ventricular arrhythmias, in the first year after MI. Thus our findings support the results of these studies.

Autonomic system imbalance with sympathetic hyperactivity and an increase in electrical instability play a specific role in patients after acute myocardial infarction, favouring life-threatening arrhythmias, increase in platelet aggregability, coronary vasoconstriction and left-ventricular wall stress. Many authors have described the protective effect of vagal activity against the development of VTAs [25, 26]. Heart rate with higher variability is the optimal state to prevent the development of fatal VTAs [27]. In our study, most patients were treated with β-blockers, with or without ACE inhibitors. The pharmacological treatment was introduced according to the patient's functional status and was independent from our study; therefore conclusions cannot be drawn on different modes of treatment in our group. β-Blockers were more frequently used in the group with higher HRV values, but the difference was not statistically significant. Lampert *et al.* [28] compared 24-h HRV parameters in patients treated with propranolol or placebo and proved that, after AMI, propranolol therapy improved recovery of parasympathetic tone, which correlated with improved outcome, and decreased sympathetic predominance in the morning. These findings may elucidate the mechanisms by which β-blockers decrease mortality.

Our study showed that very low SDNN ≤ 70 ms still has predictive value. We also analyzed non-fatal end points, but we did not find a correlation between reduced HRV and the incidence of unstable angina pectoris and MI. Some studies have indicated that early reperfusion of AMI is associated with a marked immediate recovery of HRV [18]. Also, Pedretti *et al.* [29] pointed out that early thrombolysis has a favourable effect on the cardiac sympathovagal balance, resulting in significantly reduced occurrence of arrhythmic events. Carpeggiani *et al.* [30] evaluated the in-hospital prognostic value of heart rate variability and proved the early (< 48 h) predictive value of depressed heart rate variability in the stratification of in-hospital death and major complications after acute myocardial infarction. Our study supports the opinion that even though the survival of patients significantly improved after introduction of reperfusion methods, HRV analysis still represents an important tool for outcome prediction.

Our study was limited because only time domain indices of HRV were used and there was no evaluation of the significance for frequency domain indices of HRV. Although time domain measures of heart rate variability are strongly associated with frequency domain measures [14], time domain measures do not provide specific information on the sympathetic nervous system and also depend on factors other than the autonomic nervous system [31].

In conclusion, the findings of our study support our hypothesis that, in patients treated with thrombolysis and medication administered according to state-of-the-art practice guidelines, HRV analysis still remains a helpful component of cardiac risk stratification. SDNN ≤ 70 ms should be identified as a significant marker of death after MI.

References

1. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256-62.
2. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992; 85: 164-71.
3. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction: ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998; 351: 478-84.
4. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol 1991; 18: 687-97.
5. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985; 8: 491-8.
6. Malpas SC, Maling TJ. Heart rate variability and cardiac autonomic function in diabetes. Diabetes 1990; 39: 1177-81.
7. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation 1998; 98: 1510-6.
8. Karcz M, Chojnowska L, Zaręba W, Rużyłło W. Prognostic significance of heart rate variability in dilated cardiomiopathy. Int J Cardiol 2003; 87: 75-81.
9. Sands KE, Appel ML, Lilly LS, Schoen FJ, Mudge GH, Cohen RJ. Power spectrum analysis of heart rate variability in human cardiac transplant recipients. Circulation 1989; 79: 76-82.
10. Guzzetti S, Dassi S, Pecis M, et al. Altered pattern of circadian neural control of heart period in mild hypertension. J Hypertens 1991; 9: 831-8.
11. Trojnarska O, Bręborowicz P, Łanocha M, Lesiak M, Bryl W, Cieśliński A. Heart rate variability in adult patients with congenital heart disease. Arch Med Sci 2005; 2: 98-104.
12. Roche F, Gaspoz JM, Court-Fortune I, et al. Screening of obstructive sleep apnea syndrome by heart rate variability analysis. Circulation 1999; 100: 1411-5.
13. Lelonek M, Goch JH. Heart rate variability in patients with recurrent syncope. Arch Med Sci 2006; 4: 268-73.
14. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol 1989; 64: 1162-7.
15. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. Am J Cardiol 1992; 69: 891-8.
16. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation 1993; 88: 927-34.
17. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol 1999; 34: 912-48.
18. Ortak J, Weitz G, Wiegand UK, et al. Changes in heart rate, heart rate variability, and heart rate turbulence during evolving reperfused myocardial infarction. Pacing Clin Electrophysiol 2005; 28 Suppl 1: S227-32.
19. Lanza GA, Guido V, Galeazzi MM, et al. Prognostic role of heart rate variability in patients with a recent acute myocardial infarction. Am J Cardiol 1998; 82: 1323-8.
20. Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly 2004; 134: 514-22.
21. McClements BM, Adgey AA. Value of signal-averaged electrocardiography, radionuclide ventriculography, Holter monitoring and clinical variables for prediction of arrhythmic events in survivors of acute myocardial infatrcion in the thrombolitic era. J Am Coll Cardiol 1993; 21: 1419-27.
22. Balanescu S, Corlan AD, Dorobantu M, Gherasim L. Prognostic value of heart rate variability after acute myocardial infarction. Med Sci Monit 2004; 10: CR307-15.
23. Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Circulation 1996; 94: 432-6.
24. Camm AJ, Pratt CM, Schwartz PJ, et al. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 2004; 109: 990-6.
25. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium. Influences of heart rate and vagal stimulation. Circulation 1973; 47: 291-8.
26. Myers RW, Pearlman AS, Hyman RM, et al. Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. Circulation 1974; 49: 943-7.
27. Reed MJ, Robertson CE, Addison PS. Heart rate variability measurements and the prediction of ventricular arrhythmias. Q J Med 2005; 98: 87-95.
28. Lampert R, Ickovics JR, Viscoli CJ, Horwitz RI, Lee FA. Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. Am J Cardiol 2003; 91: 137-42.
29. Pedretti RF, Colombo E, Sarzi Braga S, Caru B. Effect of thrombolysis on heart rate variability and life-threatening ventricular arrhythmias in survivors of acute myocardial infarction. J Am Coll Cardiol 1994; 23: 19-26.
30. Carpeggiani C, L'Abbate A, Landi P, et al. Early assessment of heart rate variability is predictive of in-hospital death and major complications after acute myocardial infarction. Int J Cardiol 2004; 96: 361-8.
31. Stein PK, Bosner M, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. Am Heart J 1994; 127: 1376-81.