UTILITY OF SHORT-TERM HEART RATE VARIABILITY FOR PREDICTION OF SUDDEN CARDIAC DEATH AFTER ACUTE MYOCARDIAL INFARCTION

Josef Kautzner[a], Petr Šťovíček[b], Zdeněk Anger[b], Jarmila Šavlíková[b], Marek Malik[c]

[a] *Department of Cardiology, Institute for Clinical and Experimental Medicine, Vídeňská 800, 140 00 Prague 4, Czech Republic*
[b] *Department of Medicine II, Charles University Medical School I, Unemocnice 2, 128 08 Prague 2, Czech Republic*

[c] *Department of Cardiological Sciences, St Georges Hospital Medical School, Cranmer Terrace, London SW 17 0RE, England*

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Heart rate variability (HRV) computed from 24-hour ECG recording has been associated with an increased risk of malignant arrhythmias after MI. To make HRV analysis more practical, we evaluated prospectively prognostic role of short-term HRV in comparison with other risk stratifiers.

Study population consisted of 48 patients with acute MI (mean age 59.6±10.6 years, 38 males), who were off betablockers. All patients underwent 30-minute ECG recording at supine rest on day 2 and 5 after admission, between 9 and 11 a.m. One ECG channel from a commercial bedside monitor was A/D converted, and subsequently analysed using a purpose-built interactive software. Short-term HRV was computed as the standard deviation of all normal-to-normal RR intervals (SDNN) as well as the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals (rMSSD). Left ventricular ejection fraction (LVEF, in %) was determined using 2D-echocardiography.

During one-year follow up, 5 patients (10.4 %) died of sudden cardiac death (SCD) and one of non-cardiac death. Subjects who died of SCD presented with significantly lower SDNN parameter on day 5 (28.8±4.3 vs 39±18.4, $p<0.006$) and similar trend was revealed for rMSSD (12.22.8 vs 24.321, N.S.). Similarly, LVEF was significantly decreased in these patients (35.4±5.5 vs 49.7±11.3, $p<0.007$). Positive predictive accuracy for prediction of SCD was 17 % for rMSSD, 20 % for SDNN, 29% for LVEF, and 40% for combination of depressed SDNN (≤33ms) and LVEF (≤40).

In conclusion, depressed HRV computed from short-term predischarge ECG recordings obtained under standardised conditions is associated with an increased risk of SCD. Such predictive power is substantially increased in combination with depressed LVEF, and this approach seems to be effective as a simple screening method to identify high risk subjects.

INTRODUCTION

Despite a continuing decrease in mortality following acute myocardial infarction, arrhythmic cardiac death remains the most common cause of death in industrialised countries[1]. Even in the thrombolytic era, estimated one-year total mortality among survivors of acute phase of myocardial infarction varies around 5% (ref. [2–3]). Most importantly, the majority of these deaths is of arrhythmic origin and about half of them occurs during the first 3 to 6 months of follow up. This provides a background for the concept of risk stratification early after acute myocardial infarction[4]. Based on retrospective analyses of various risk stratification techniques in post-infarction population, arrhythmic death was found to be associated predominantly with depressed heart rate variability (HRV) in 24-hour recordings, while non-arrhythmic death was more related to low left ventricular ejection fraction (LVEF)[5,6]. However, clinical utility of HRV analysis from conventional 24-hour recordings is limited by multiple factors such as the cost of the equipment, laborious editing of the recorded data, possible technical artefacts, and methodological difficulties regarding analysis itself. To make HRV analysis more practical, we evaluated prospectively prognostic role of short-term ECG recordings obtained under standardised conditions from a commercial bed-side monitor in comparison with an echocardiographic estimate of LVEF in a cohort of survivors of acute phase of myocardial infarction. In addition, we studied the potential prognostic value of plasma catecholamine levels as a measure of sympathoadrenal activation, and their relationship to HRV.

METHODS

From a consecutive series of patients admitted to the coronary care unit with a diagnosis of acute myocardial infarction, 48 subjects, who fulfilled inclusion criteria, entered the study (mean age 59.6±10.6 years). All of them were admitted within 24 hour from the beginning of symptoms. Acute myocardial infarction was defined according to the World Health Organisation criteria[7]. Haemodynamically unstable patients and those with supraventricular arrhythmias, sinus node dysfunction or pacemaker implant were not included into the study. The

age > 75 years and significant diabetes mellitus were another exclusion criteria. None of the patients were receiving antiarrhythmic drugs, catecholamines or beta-blockers during the course of the study, i.e. from hospital admission to day 5. Patients were followed up in outpatients, with telephone inquiry to determine the fate of non-attenders. If patient died, the precise circumstances of death were evaluated in co-operation with the relatives and attending physician. The follow up period was one year.

All patients underwent 30-minute ECG recording in supine position when resting in bed. The recordings were obtained on day 2 and 5 following hospital admission, always between 9 to 11 a.m. after 30-minute resting period. One-channel ECG from commercial bed-side monitor (Hewlett-Packard) was recorded, A/D converted and saved on hard disk of personal computer. Automatic detection and labelling of the QRS complexes were performed using a purpose-built interactive software. All labelled QRS complexes were checked by the operator. Short-term HRV was computed as the standard deviation of all normal-to-normal RR intervals (i.e. NN intervals) of the 30-minute recording (SDNN parameter) and/or as the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals (rMSSD parameter).

All patients had an intravenous cannula inserted in peripheral vein approximately 30-minutes before the start of the recording. Ten millilitres blood samples were drawn immediately after the period of ECG recording into chilled syringes. For plasma catecholamine analysis, samples were collected into chilled tubes containing ethyleneglycoltetraacetic acid and glutathione. Tubes were placed on ice, centrifuged and plasma samples were stored below –20 °C until analysed. Epinephrine, norepinephrine and dopamine plasma levels were assessed using radioenzymatic assay (Catechola, UVVR, Prague, Czech Republic) and the results are expressed in pmol/mL.

LVEF was determined within one week of infarction. 2D-echocardiography was employed to assess the ejection fraction using planimetric method.

Comparison of continuous data was performed using the paired or non-paired Student's t test, when appropriate. Pearson correlation coefficients were used to assess the relation of catecholamine levels to HRV parameters. Results are expressed as mean±SD. A value of $p < 0.05$ was required for statistical significance. Sensitivity was defined as the proportion of patients with sudden death that had a positive test (i.e. true positive/true positive plus false negative). Specificity was defined as the proportion of patients without arrhythmic death that had a negative test (i.e. true negative/true negative plus false positive). Positive predictive accuracy was defined as the proportion of patients with a positive test that succumbed to sudden death.

RESULTS

The basic clinical characteristics of the study population are summarised in Table 1. Most of the patients presented with Q-wave infarct (85.4 %) and were administered streptokinase within the first 6 hours of the onset of chest pain (79.2 %). The mean LVEF was 48.2±11.6 % (range 24–65 %). No significant difference in basic characteristics was found between patients with anterior and inferior infarction. There were 5 (10.4 %) sudden, presumably arrhythmic, cardiac deaths (SCD). None of the patients experienced sustained ventricular tachycardia. Another patient died of complication of acute peripheral arterial closure.

Table 1. Basic Clinical Characteristics of the Study Population

Parameter	Mean±SD	Range
men/woman	38/10 (79.2/20.8 %)	
age (years)	59.6±10.6	37–77
diabetes mellitus	13 (12.5 %)	
previous MI	9 (18.8 %)	
anterior/inferior MI	18/30 (37.5/62.5 %)	
Q/non-Q MI	41/7 (85.4/14.6 %)	
peak creatin kinase (μmol/L)	37.5±17.4	4.5–85
thrombolytic therapy	38/10 (79.2/20.8 %)	
LV ejection fraction (%)	48.2±11.6	24–65

Despite an apparent decrease in the mean heart rate between day 2 and 5 of hospital admission (mean NN interval 797±123 vs. 838±108 ms, $p<0.033$), no significant difference in HRV parameters was found. Patients with anterior infarction had faster heart rate on day 2 (749.6±81.1 vs. 841.1±136.8 ms, $p<0.009$) and this difference disappeared on day 5. Accordingly, anterior localisation of myocardial infarction was associated with significantly lower HRV on day 2 as compared to inferior infarction. The difference in HRV was still present on day 5, although statistically non-significant (Table 2). Subjects who died suddenly during one-year follow up presented with significantly lower heart rate on day 2 while no significant difference was revealed on day 5. On the contrary, sudden cardiac death victims had significantly depressed SDNN parameter on day 5 and similar trend was found for rMSSD parameter, however, the difference did not reach statistical significance (Table 3). When

Table 2. Heart Rate and Heart Rate Variability Values According to Infarct Site

Parameter	Anterior MI	Inferior MI	p <
Day 2			
mean NN interval (ms)	749.6±81.1	841.1±136.8	0.009
rMSSD (ms)	15.5±8.3	24.4±13.3	0.01
SDNN (ms)	36.0±11.3	46.5±20.6	0.038
Day 5			
mean NN interval (ms)	821.0±85.8	858.0±125.3	N.S.
rMSSD (ms)	17.1±13.5	26.7±23.9	N.S.
SDNN (ms)	33.2±13.1	42.0±20.5	N.S.

rMSSD – square root of the mean of the sum of the squares of differences between adjacent normal RR intervals, SDNN – standard deviation of all normal-to-normal RR intervals (i.e. NN intervals)

Table 3. Prognostic Value of Individual Parameters

Parameter	Sudden Cardiac Death (n = 5)	Alive (n = 42)	p <
Age (years)	57.2±11.6	59.5±10.4	N.S.
Creatin kinase (mol/L)	35.4±17.1	31.1±17.8	N.S.
CK-MB (mol/L)	2.8±1.4	2.8±1.8	N.S.
LVEF (%)	35.4±5.5	49.7±11.3	0.007
Day 2			
Epinephrine (pmol/mL)	0.23±0.17	0.47±0.99	N.S.
Norepinephrine (pmol/mL)	2.8±2.3	1.7±1.5	N.S.
Dopamine (pmol/mL)	0.66±0.4	0.5±0.4	N.S.
Mean NN (ms)	689.1±73.5	810.6±121.3	0.035
rMSSD (ms)	16.2±11.9	21.5±12.4	N.S.
SDNN (ms)	38.0±17.8	41.8±18.0	N.S.
Day 5			
Epinephrine (pmol/mL)	0.14±0.05	0.27±0.44	N.S.
Norepinephrine (pmol/mL)	1.0±0.4	1.1±0.7	N.S.
Dopamine (pmol/mL)	0.81±1.2	0.34±0.23	N.S.
Mean NN (ms)	800.7±89.3	844.6±110.1	N.S.
rMSSD (ms)	12.2±2.8	24.3±21.0	N.S.
SDNN (ms)	28.8±4.3	39.0±18.4	0.006
CK-MB – creatin kinase MB fraction, LVEF – left ventricular ejection fraction, other abbrevitaions as in Table 2.			

Table 4. Plasma Catecholamine Levels

Parameter	Day 2	Day 5	p <
Epinephrine (pmol/mL)	0.44±0.9	0.26±0.4	0.015
Norepinephrine (pmol/mL)	1.8±1.6	1.1±0.6	0.0001
Dopamine (pmol/mL)	0.53±0.4	0.41±0.5	0.022

LVEF was considered, subjects who succumbed to sudden cardiac death within one year of follow up had significantly lower LVEF as compared to the survivors (Table 3).

Plasma catecholamine levels decreased from day 2 to 5 of acute myocardial infarction (Table 4). No differences between anterior and inferior localisation of myocardial infarction were found. Similarly, no significant correlation was revealed between either of plasma catecholamine levels and LVEF and/or HRV parameters (Figure 1). More importantly, no significant difference in plasma catecholamines was found between subjects who subsequently died of sudden death and the survivors (Table 3).

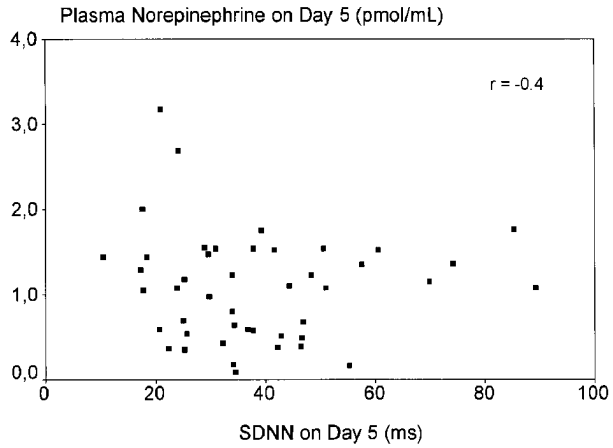

Fig. 1. An example of the relationship between plasma catecholamines (in this case norepinephrine on day 5) and short-term HRV (represented by SDNN parameter on day 5). No significant correlation between both variables was found.

Table 5. Value of Prognostic Variables in Predicting Sudden Cardiac Death

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)
rMSSD Day 5 ≤ 15	80	53	17
SDNN Day 5 ≤ 33	80	62	20
LVEF ≤ 40	80	75	29
LVEF ≤ 40 and rMSSD Day 5 ≤ 15	80	83	33
LVEF ≤ 40 and SDNN Day 5 ≤ 33	80	86	40
Abbreviations as in Table 2 and 3.			

The sensitivity, specificity, and positive predictive accuracy of the prognostic tests in prediction of risk of sudden death are shown in Table 5. Because of an independent nature of HRV indices and LVEF, combinations of variables were evaluated. It is apparent that short-term HRV retains predictive power which is lower as compared to that of LVEF. Combination of HRV parameters and LVEF was associated with improvement of predictive value.

DISCUSSION

The major findings of this study can be summarised as follows: (1) sudden cardiac death occurred within 12 months of follow up in 5 subjects (10.4 %), (2) victims of sudden cardiac death presented with significantly lower SDNN computed from short-term recordings on day 5 of acute myocardial infarction, and with depressed LVEF, (3) plasma catecholamine levels were not predictive of subsequent arrhythmic events, (4) combination of lower short-term SDNN on day 5 (≤33 ms) and depressed LVEF (≤40 %) led to significant improvement of predictive power (positive predictive accuracy of 40 %) in estimating risk of SCD.

Decreased HRV has been associated with poor prognostic outcome in patients after acute myocardial infarction and with the occurrence of major arrhythmic events in particular[8–11]. However, difficulties associated with reliable analysis of 24-hour ECG recordings and the need for laborious editing led to some retrospective studies concerning clinical utility of HRV assessed from short-term (i.e. up to 30 minutes) recordings[12,13]. It has been demonstrated that such approach might be useful for predischarge screening of high risk population[13].

The results of this study confirm the above preliminary data obtained from short ECG recordings extracted from 24-hour electrocardiograms. Using a simple set-up for one-channel ECG recording and ensuring comparable recording conditions, short-term HRV measures were found predictive of outcome during one-year follow up. Specifically, significant depression of SDNN obtained on day 5, i.e. before hospital discharge, was revealed in subjects who subsequently died of sudden cardiac death as compared to those survivors. For rMSSD the decrease did not reach statistical significance. When compared with LVEF, specificity and positive predictive accuracy of both HRV measures were found lower. This is at variance with previous studies using 24-hour HRV, which was demon-

strated predictive of arrhythmic events, while LVEF predicted more accurately total mortality[5,6]. Such finding may not be surprising as the information about circadian variation in heart rate is believed to be crucial for more accurate prediction of arrhythmic events[14]. Therefore, our data suggest that although it is not possible to replace HRV measures obtained from long-term recordings, the simple short-term recordings may be useful in predischarge screening and selection of subjects for subsequent use of more comprehensive and costly stratification techniques. More importantly, the predictive value of short-term HRV may further be improved in combination with depressed LVEF (≤40 %). The resulting positive predictive accuracy of 40 % should identify high risk patients very effectively. Therefore, this approach may prove to be both cost and time effective method for practical application of HRV in future clinical trials on prophylaxis of sudden cardiac death after acute myocardial infarction.

In addition, we found relationship between short-term measures of HRV and infarct site. Specifically, HRV was lower in anterior as compared to inferior infarction in the early phase of infarction. In predischarge recordings, the difference was less pronounced. Based on our previous studies using spectral analysis of short-term recordings[15], differences between anterior and inferior wall infarction favour the hypothesis about vagal hyperactivity during acute phase of inferior infarction which disappears during the first week. Such vagal hyperactivity may represent reflex increase from vagal afferent nerves in inferior infarction[16] and was also suggested when analysing 24-hour recordings obtained immediately after hospital admission[17,18]. Disappearance of these early differences later in the healing phase seems to be consistent with data obtained from predischarge recordings[10]. This finding is in accordance with observation of Pipilis et al.[17], while most previous studies revealed no such a difference. However, these studies were mainly focused on HRV measured later in the course of infarction. Therefore, our data further emphasise that reliable short-term HRV analysis for the purpose of risk stratification studies may be expected after several days of hospital stay.

Clinical and experimental data suggest that sympathoadrenal activation after acute myocardial infarction may contribute to subsequent mortality[19–21]. In the early studies, the magnitude of plasma catecholamine response early in the course of infarction was shown to be related to the extent of myocardial damage and late mortality. Our data confirmed initial sympathoadrenal activation with subsequent drop in the plasma catecholamine levels and no relationship to HRV parameters. Similarly, no difference in the magnitude of sympathoadrenal activation was revealed between patients who died suddenly and the rest of the group. This is compatible with our previous observation[15], that increased plasma levels of norepinephrine rather reflect the presence of myocardial ischaemia and/or necrosis per se, independently on the site of myocardial infarction.

The small number of patients, and the short follow up duration represent the major limitation to this study. Therefore, the results may not be extrapolated to other populations. However, the results are comparable to those obtained from retrospective analyses of large series of postinfarction patients. Also clinical characteristics of study population appear to be comparable to other postinfarction risk stratification trials. Only the proportion of SCD cases was relatively high, reaching around 10 % of the study population.

In conclusion, depressed short-term HRV obtained under standardised conditions is associated with increased SCD mortality in patients following acute myocardial infarction. However, predictive power of short-term HRV analysis is lower than that reported for analysis of 24-hour recordings and thus, easily obtainable short-term HRV measures may be used only for screening of high risk patients. On the contrary, plasma catecholamines do not differentiate between patients with high and low risk of SCD. Combination of short term HRV with echocardiographic estimate of LVEF significantly improves the positive predictive accuracy of HRV itself, and these two simple methods may prove cost-effective and practical for future clinical trials on prophylaxis of sudden cardiac death after acute myocardial infarction.

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