HEART RATE VARIABILITY AS A PREDICTOR OF ADVERSE PROGNOSIS IN PATIENTS WITH UNSTABLE ANGINA PECTORIS AND CONCOMITANT DIABETES MELLITUS

Trigulova R.K., Kurbanov R.D.

Republican Tertiary Center of Cardiology under the Ministry of Health of the Republic of Uzbekistan, Tashkent, e-mail: Irina.Ivanova2@nycomed.com

To assess informative value of heart rate variability (HRV) parameters in late-term prognosis in patients with unstable angina pectoris and concomitant type 2 diabetes mellitus. 31 patients with newly diagnosed and progressing angina pectoris followed-up for 2 years were examined. Upon 24-hour monitoring disorders in heart rate and conduction as well as heart rate variability parameters were assessed. Fatal and non-fatal myocardial infarction, sudden death, emergent rehospitalization were among the adverse outcomes. For patients with both adverse and favorable courses statistically confident differences were observed in minimum heart rate values (P = 0,039) and SDNN5 (P = 0,04) by the 2nd week of treatment. SDNN < 68 ms ($\chi 2 = 2,97$, P = 0,046) and SDNN5 < 30 ms ($\chi 2 = 2,97$, P = 0,046) were shown to serve as predictors of the disease unfavorable course revealed on the 2nd week of treatment. SDNN > 98 ms ($\chi 2 = 4,4$, P = 0,036) registered by the 2nd week of treatment turned out rззук limit confidently discriminating patients with angina pectoris adverse and favorable course. ECG Holter monitoring results, parameters characterizing HRV, in particular, can serve as additional predictors of adverse prognosis in patients with UAP and concomitant type 2 diabetes mellitus.

Keywords: unstable angina pectoris, type 2 diabetes mellitus, ECG Holter monitoring, transitory iscahemia, heart rate variability

Association of unstable angina pectoris (UAP) with high risk of myocardial infarction and lethal outcome because of ischaemic heart disease (IHD) makes researchers pay more attention to risk stratification of UAP patients to assess both early and late outcomes [1]. ECG Holter monitoring is a method for risk stratification of myocardial infarction survivors. Studies in patients with UAP are scarce, their findings being discrepant [2-7]. Studies on the problem in UAP patients with type 2 diabetes mellitus are even scarcer [8].

Our study aimed at assessment of informative value of heart rate variability (HRV) parameters in determination of late-term prognosis in patients with UAP and concomitant type 2 diabetes mellitus (type 2 DM).

Materials and methods of research

The study was open, observational with retrospective analysis. We followed-up 31 patients referred to Ischaemic Heart Disease Department at … with diagnosis of IHD, unstable angina pectoris.

Typical manifestations of UAP onset or progression in compliance with the European Society of Cardiology recommendations [6] as well as presence of registered type 2 DM (WHO, 1999) were the criteria for inclusion.

Acute myocardial infarction (AMI) for less than 3 months, type 2 DM severe decompensation requiring insulin therapy, III-IV functional class complex chronic cardiac insufficiency (CCI), coronary arteries revascularization in medical history as well as severe hepatic and renal dysfunctions met the criteria for exclusion.

Mean age of patients was 54 ± 1,08 year. Acute myocardial infarction (AMI) and arterial hypertension were found in medical history of 65,8% and 52,4% of the examinees, respectively. Type 2 DM and IHD duration was 5,4 ± 0,69 and 6,3 ± 0,88 years, respectively.

The study included one in-patient stage (I) and three out-patient stages to follow up the patients after discharge for 14-15 days (II), for 1 month (III) and for 3 months (IV) with 12-month and 24-month periods of further clinical follow up.

All patients had their demographic IHD risk factors and clinical characteristics, such as, pain syndrome dynamics a week before hospitalization, as well as hemodynamic parameters, such as heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP), left ventricular systolic and diastolic parameters and resting ECG monitoring assessed. All patients underwent 24 – hour ECG Holter monitoring (ECG HM) within first 24 hours starting from the moment of inclusion into the study. Disorders of cardiac rhythm and conduction as well as heart rate variability (HRV) parameters were assessed in 24-hour monitoring. Patients with complex cardiac rhythm disorders were excluded. We assessed time and geometric characteristics of HRV, including SDNN (ms) – Standard Deviation of Normal-to-Normal RR intervals, SDNN5 (ms) – Mean of the Standard Deviations of all Normal-to Normal RR intervals for all 5-minute segments, SDANN (ms) – Standard Deviation of Averaged Normal-to-Normal RR intervals, PNN-50 (%)-Percentage of differences between adjacent NN intervals that are > 50 ms, HRVi – Heart Rate Variability triangular index (standard units), RMSSD (ms) – the square Root of the Mean of the Sum of the Squares of Differences between adjacent RR intervals [9]. Data on patients with the assessed myocardial infarction episodes in the form of depression or ST segment elevation, constituting separate part of the study were published earlier [10].

Complete lipid profile was determined by standard methods [11]. Friedewald formula was used to measure concentrations of low density lipoprotein (LDL) cholesterol [11]. Fasting and postprandial glycemia as well as glycated hemoglobin were the carbohydrate metabolism parameters to measure [12, 13]. Upon discharge all patients had their IHD clinical course, ECG HM and blood glucose assessed.

Basic therapy included anticoagulants (heparin) (100%) at the acuity, aspirin (100%), beta-adrenergic blockers (100%), nitrates (95%), APE inhibitors (95%) and atorvastatin (100%). To correct carbohydrate metabolism all patients received glybenclamide in the dose 5 ± 0,25 mg/d. By the end of 2-year follow-up the pa-

tients were divided into 2 groups. Patients with the disease favorable and adverse course were included into the 1st ($n = 21$, 67,7%) and the 2nd group ($n = 10$, 33,2%), respectively. Fatal and non-fatal myocardial infarction, stroke, sudden death, emergent rehospitalization were among the adverse outcomes. Three patients had non-fatal acute myocardial infarction, urgent revascularization due to unsatisfactory drug therapy being performed in one, angina destabilization episodes with the transfer to lower functional class taking place in seven.

The results were processed with the standard analysis of variation by means of Student test for quantitative parameters and χ^2 criterion (Statistica, version 6,0).

When searching for prognostic criteria of the unstable angina adverse outcome we looked up to statistical parameters flagging confident intergroup differences in a characteristic frequency of occurrence in the groups compared (in terms of χ^2 criterion) as well as to maximum value of occurrence ratio reflecting discriminating power of the characteristic analyzed. Intergroup differences were confident at $P < 0,05$,

Results of research and their discussion

Patients of both groups were comparable by the IHD precipitating signs (table).

Incidence of IHD adverse course factors in patients with UAP and concomitant type 2 DM with favorable and adverse outcomes, abs (%)

Sign	All patients (%)	1st group	2nd group	χ2	P value
AMI documented in medi-cal history	19 (64)	11 (54,2)	8(80)	1,472	0,225
Arterial hypertension	17 (54)	12 (57)	5 (59)	0,00	0,9
Dyslipidemia	25 (80,6)	16 (76)	9 (85)	0,179	0,672
Smoking	23 (74,1)	15 (70)	8 (81)	0,005	0,944
Age > 60 years	7 (22,5)	4 (18,7)	3 (30)	0,179	0,672
Type 2 DM duration 5 and more years	18 (58)	10 (47)	8 (81,2)	1,739	0,187
LV hypertrophy (ECG signs)	12(38,7)	6(30,9)	6(61)	1,651	0,199
SBP > 160 mm Hg (at hospitalization)	10(32,2)	6(28,6)	4(42,1)	0,051	0,822
DBP > 100 Hg (at hospitalization)	10 (32,2)	6 (28,6)	4 (42,1)	0,051	0,822
HR > 90 beats/min (at hospitalization)	13 (41,9)	9(42,5)	4(30,4)	0,157	0,811
Cardiac rhythm disorders requiring antiarrhythmics	0(0)	0(0)	0(0)	0(0)	0(0)
LV systolic function (EF < 40%)	0(0)	0(0)	0(0)	0(0)	0(0)
Patients with UAP	31(100)	21 (67,7)	10 (32,2)		

Note: EF – ejection fraction;
*P < 0,05 statistic significance in relation to the group of patients with the disease favorable course.

As per results of ECG HM performed basally, that is, at the disease acuity in patients of two groups, respectively, mean minimum HR values were 53,1 ± 2,41 and 53,6 ± 4,41 beats/min ($t = 0,11$; $P = 0,9$), mean maximum HR values being 104,7 ± 2,52 and 103,0 ± 4,9 beats/min ($t = 0,34$; $P = 0,73$), mean SDNN values were registered 97,5 ± 7,25 and 90,7 ± 13,65 ms ($t = 0,46$; $P = 0,63$), mean SDNN5 values being 47,2 ± 4,38 and 39,1 ± 4,95 ms ($t = 1,12$; $P = 1,12$); mean SDANN values were 91,4 ± 5,19 and 85,1 ± 11,61 ms ($t = 0,58$; $P = 0,57$), HRVi being 418,9 ± 45,65 and 415,1 ± 58,39 standard units, ($t = 0,05$; $P = 0,96$). Thus, no HRV parameter documented basally demonstrated statistically confident differences in the mean values above.

Results of ECG HM performed on the 2nd week of treatment (2-week ECG HM) showed statistically confident differences in two mean values of parameters between patients of the 1st and 2nd group. These were mean minimum HR (50,7 ± 1,15 beats/min in patients with the disease favorable course versus 56,1 ± 2,74 beats/min in those with the disease adverse course, $t = 2,16$; $P = 0,039$) and mean SDNN5 (52,0 ± 3,68 ms in the 1st group patients versus 38,1 ± 2,28 ms registered in the 2nd group patients, $t = 2,15$; $P = 0,004$). A tendency to statistically confident differences between patients with the disease favorable course (114,1 ± 9,82 ms) and those with the adverse disease (87,8 ± 11,45 ms) was found in SDNN dynamics ($t = 1,6$; $P = 0,12$).

Due to variability of the values no confident differences in other parameters registered at this stage of observation were registered. Thus, mean values of maximum HR were 103,6 ± 1,82 versus 99,7 ± 13,65 beats/min ($t = 1,103$; $P = 0,28$), mean SDANN values being registered 97,9 ± 4,59 ms versus 81,1 ± 11,38 ms ($t = 1,65$; $P = 0,11$); mean HRVi values were 413,7 ± 362,9 standard units versus 354,1 ± 46,01 standard units ($t = 0,95$; $P = 0,35$).

Analysis of values obtained basally demonstrated absence of any informative HRV markers to predict IHD adverse or favorable course.

2 weeks later SDNN < 68 ms was registered in 30% of patients with the adverse IHD and in none of those with its favorable course (0%, $\chi 2 = 2,97$, $P = 0,046$). Similar regularity, that is, 30% (2^{nd} group) versus 0% (1^{st} group) was established in SDNN5 dynamics (< 30 ms).

2 week ECG HM registered SDNN > 98 ms happened to be upper limit confidently discriminating patients with the IHD favorable and adverse courses. It was established in 57,4% of the former and only in 10 patients of comparison group (10%, $\chi 2 = 4,4$, $P = 0,036$), that is, 5 times less frequently. Thus, SDNN turned out the most valuable for differentiation of patients with the disease favorable and adverse courses.

When searching for detrimental IHD markers we found out that the parameters of an organism's system activities abnormalities of which could be easily explained from the disease pathogenesis point of view are of ultimate interest. Parameters of cardiac autonomous regulation are among them. To assess cardiac autonomous regulation we used ECG Holter to study heart rate variability. In previous publications [10] we managed to demonstrate that in the non-diabetics with unstable angina pectoris frequency and character of transitory ischaemia are independent of HRV, in the presence of diabetes mellitus and reduced HRV mean duration of painless ischaemia being two times greater than the one of painful myocardial ischaemia. As to mean values of all time HRV parameters, no differences between the group of UAP patients with diabetes mellitus and the one of UAP non-diabetics were found, though *apriori* we expected to observe more marked disorders of autonomous heart rate regulation in the former. The findings are a continuation to the analysis of data obtained as a result of 2 – year follow-up of the patients and the disease course.

As per results of ECG Holter performed in patients of our sample basally, that is, at the disease acuity, we failed to discriminate patients with the disease adverse and favorable courses. This can be possibly associated with the necessity to take into account on the day of hospitalization too many factors affecting the parameters to be studied in a patient with acute cardiac crisis.

Following the grouping of patients as per 2-week ECG Holter monitoring results confidently higher HRV values in the 2nd group patients were registered indicating predominance of sympathicotonia in this category.

In addition, mean SDNN5 values turned out confidently lower in the 2nd group than in the 1st one to be the evidence for HRV reduction. SDNN < 68 ms and SDNN5 < 30 ms discriminating patients with the disease adverse and favorable course turned out cut-off minimum values registered almost in one third of patients with the adverse IHD, but in none of those with the disease favorable course. SDNN > 98 ms, registered on the 2nd week of observation, turned out the upper limit confidently discriminating patients with adverse and favorable IHD. It was established to occur in more than a half of patients with favorable course, that is, 5 times more frequently than those with adverse IHD. Closeness of the parameter to favorable proggnosis cut-off value (100 ms) obtained in other categories of patients [15, 16] is possibly the evidence for universality and high practical value of the parameter in risk stratification. SDNN is a universally recognized parameter with the highest specificity and sensitivity as compared with other IHD lethal outcome predictors [14]. ECG Holter monitoring started in patients with unstable angina pectoris within first 24 hours after the last pain attack demonstrated all HRV time parameters confidently lower than those in healthy subjects of the same age and closer (though somewhat higher) to those observed in persons suffering myocardial infarction.

Conclusions

1. Analysis of basal ECG Holter monitoring parameters detected no informative HRV markers to predict either adverse or favorable IHD course.
2. Assessment of ECG Holter monitoring performed on the 2^{nd} week of treatment showed intergroup differences in mean minimum values of heart rate and SDNN5,
3. SDNN < 68 ms and SDNN5 < 30 ms turned out cut-off minimum values discriminating patients with IHD adverse and favorable course after angina pectoris destabilization.
4. SDNN > 98 ms registered by the 2^{nd} week of treatment turned out high limit confidently discriminating patients with angina pectoris adverse and favorable course.

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