Evaluation of 5-Year Risk of Cardiovascular Events in Patients after Acute Myocardial Infarction Using Synchronization of 0.1-Hz Rhythms in Cardiovascular System

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Background: Synchronization between 0.1-Hz rhythms in cardiovascular system is deteriorated at acute myocardial infarction (AMI) leading to a disruption of natural functional couplings within the system of autonomic regulation.

Objective: This study evaluates the prognostic value of autonomic regulation indices for the 5-year risk of fatal and nonfatal cardiovascular events in patients after AMI.

Methods and Results: We studied 125 patients (53 [42%] female) after AMI aged between 30 and 83 years. The period of observation was 5 years with checkpoints at the first week after AMI and after each year after AMI. We compared the prognostic value of established clinical characteristics and degree S of synchronization between 0.1-Hz rhythms in heart rate and microcirculation for evaluation of the 5-year risk of mortality and recurrent myocardial infarction (MI) in patients after AMI. Acute heart failure Killip 2–4 at AMI and S < 20% at the first week after AMI were identified as the most important factors for evaluation of the risk of 5-year mortality in patients after AMI ($\chi^2 = 14.2$, $P = 0.003$). Sensitivity and specificity of low S (<20%) at the first week after AMI were 76% and 43%, respectively. For evaluation of the 5-year risk of recurrent MI index S had no advantage over established clinical characteristics.

Conclusion: The value of S below 20% in patients with AMI is a sensitive marker of high risk of mortality during the subsequent five years. It is characterized by better prognostic value than most of established clinical characteristics.

Ann Noninvasive Electrocardiol 2012;17(3):204–213

acute myocardial infarction; risk factors; 0.1-Hz rhythms

Heart rate variability (HRV) is a readily available marker of autonomic dysfunction that affords important information for prognosis of cardiovascular events in patients after acute myocardial infarction (AMI).[1–8] It surpasses even left ventricular systolic dysfunction in reliability of prognosis of mortality.[9,10]

Along with classical methods of HRV evaluation different nonlinear methods are used recently in clinical practice for studying autonomic

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This study was supported by the Russian Foundation for Basic Research, Grant No. 10–02–00980.

The authors have no conflicts of interest.

DOI:10.1111/j.1542-474X.2012.00514.x

regulation of cardiovascular system (CVS). It is known that various rhythmic processes interacting with each other govern operation of human CVS.[11,12] Among them are the rhythms with a basic frequency of about 0.1 Hz observed in HRV,[11–13] arterial pressure,[11,12,14] and microcirculation.[15,16] According to one hypothesis, these rhythms have a central origin and represent an intrinsic property of autonomous neural network.[15,17–19] On another hypothesis the 0.1-Hz rhythms are largely an index of baroreflex gain.[20,21] It has been found that 0.1-Hz rhythms can be synchronized between themselves.[16,22] Optimal adjustment between these low-frequency (LF) rhythmic processes resulting in their internal synchronization ensures a high adaptability of CVS that is necessary for global healthy behavior of the organism. However, this synchronization is deteriorated at AMI leading to a disruption of natural functional couplings within the system of CVS autonomic regulation.[16,22] Note that features of blood flow in skin microcirculation can serve as a reliable marker of blood flow in large arteries, for instance in humeral artery.[23]

The current study was designed to evaluate and compare the ability of different clinical characteristics and degree S of synchronization between 0.1-Hz rhythms in heart rate and microcirculation to predict fatal and nonfatal cardiovascular events in patients after AMI within the 5-year period.

METHODS

Study Setting and Patient Selection

The study was approved by the Ethics Committee of the Saratov Research Institute of Cardiology in Saratov, Russia, and informed consent was obtained from all participants. Our study included 125 post-AMI patients (53 [42%] females and 72 [58%] males) aged between 30 and 83 years. Baseline characteristics of patients are shown in Table 1.

The period of prospective observation of patients was 5 years between 2004 and 2009 with checkpoints at the second–fourth day after AMI and after each year after AMI. Death and myocardial infarction (MI) were defined as end points of observation. Composite end points, for example, death/MI or MI at 1 year and death at 5 years were also considered. If MI was not the reason of death, we differentiated the cases of sudden death without pathologoanatomic study and death as the result of complication of attendant diseases.

During hospitalization all post-AMI patients were treated in accordance with contemporary recommendations for acute coronary syndrome treatment. The list of medications used in therapy is given in Table 1. To study autonomic control of CVS at the first week after AMI we carried out spectral analysis of HRV and estimated degree of synchronization between 0.1-Hz rhythms in heart rate and microcirculation.

Electrocardiogram (ECG), photoplethysmogram (PPG) measured on the middle finger of the subject's hand and respiration were simultaneously recorded in a supine resting condition under spontaneous breathing. The signals were recorded during the first week after AMI (at the second–fourth day after AMI) between 13 and 15 hours. The duration of each record was 10 minutes. All signals were sampled at 250 Hz and digitized at 14 bits. The record of respiration was used to control evenness of breathing. We excluded from the analysis the series with forced inspiration and delays in breathing. For further analysis only ECG and PPG records without artifacts, extrasystoles and considerable trends were left. If the records did not satisfy the mentioned criteria, we performed new measurements to obtain the records suitable for further analysis. As the result, we had the data from all 125 post-AMI patients relevant for our study. All the patients were hemodynamically stable at the time of measurement after 1–5 years after AMI.

Statistical Analysis

Continuous variables are reported as medians with interquartile ranges, Table 1. Categorical data are presented as frequencies and percentages. The Kaplan–Meier survival curves, Cox's regression models, F-criterion and odds ratio (OR) were used to assess the ability of different autonomic control indices to evaluate the 5-year risk of death and recurrent MI in patients after AMI. The prognostic features of the considered indices were compared. The obtained estimations were considered statistically significance if $P < 0.05$. The interdependence between the indices was assessed basing on paired correlations and multiple regression.

We estimated the ratio of the odds of mortality or recurrent MI occurring in one group of post-AMI patients to the odds of their occurring in another

Table 1. Baseline Characteristics of 125 Patients with AMI

Parameter	All Patients (n = 125)
Age, years, median (Q1, Q3)	65 (57, 74)
Female sex, no. (%)	53 (42)
Myocardial ischemia, stenocardia, no. (%)	99 (79)
Prior myocardial infarction, no. (%)	59 (47)
Remoteness of prior myocardial infarction, years, median (Q1, Q3)	3 (1, 8)
Chronic heart failure, no. (%)	46 (37)
Hypertension, no. (%)	78 (62)
Remoteness of hypertension, years, median (Q1, Q3)	10 (5, 20)
Prior stroke, no. (%)	9 (7)
Peripheral vascular disease, no. (%)	2 (2)
Chronic hepatic failure, no. (%)	4 (3)
Diabetes	11 (9)
Chronic obstructive disease of lungs, no. (%)	14 (11)
Current or previous smokers, no. (%)	28 (22)
Acute coronary syndrome with ST elevation, no. (%)	80 (64)
Pathological Q wave on ECG, no. (%)	79 (63)
Acute heart failure, Killip 2–4, no. (%)	12 (10)
In-hospital lethality, no. (%)	2 (2)
Complicated myocardial infarction, no. (%)	15 (12)
Baseline systolic blood pressure, mmHg, median (Q1, Q3)	140 (120, 160)
Baseline diastolic blood pressure, mmHg, median (Q1, Q3)	85 (80, 90)
Body mass index, median (Q1, Q3)	27.7 (24.8, 29.3)
Total cholesterol, mg/dL, median (Q1, Q3)	189 (166, 218)
Triglycerides, mg/dL, median (Q1, Q3)	99 (86, 130)
Creatinine, mg/dL, median (Q1, Q3)	0.79 (0.76, 0.82)
Left ventricular ejection fraction,%, median (Q1, Q3)	50 (46, 57)
LF HRV, ms^2, median (Q1, Q3)	127 (51, 313)
HF HRV, ms^2, median (Q1, Q3)	181 (79, 438)
Index S of synchronization between 0.1-Hz rhythms, median (Q1, Q3)	16 (9, 25)
Trombolysis, no. (%)	40 (32)
Anticoagulants, no. (%)	121 (97)
Antireagents, no. (%)	125 (100)
Beta-adrenoceptor blockers, no. (%)	105 (84)
Angiotensin-converting enzyme inhibitors, no. (%)	115 (92)
Calcium antagonists, no. (%)	8 (6)
Diuretics, no. (%)	54 (43)
Cardiac glycosides, no. (%)	3 (2)
Statins, no. (%)	9 (7)

group of post-AMI patients differed from the first group by the values of risk factors.

Cox's regression models of proportional intensities were used for multivariate analysis of dependence of the probability of the considered fatal or nonfatal cardiovascular event on various risk factors. These models can be applied to variables with different shape of probability distribution. The model has the following form:

$$h\left\{(t), (z_1, \ldots, z_m)\right\} = h_0(t) \exp\left(\beta_1 z_1 + \cdots + \beta_m z_m\right),$$

where h is the resulting intensity at the time moment t and given covariates $z_1, \ldots, z_m$, h_0 is the basic intensity function, which is equal to the intensity if all the independent variables are equal to zero, and $\beta_1, \ldots, \beta_m$ are the regression coefficients.

Spectral characteristics of HRV were calculated using parametric method of spectrum estimation based on autoregression model construction. High-frequency (HF) range, 0.15–0.4 Hz, and LF range, 0.04–0.15 Hz, of HRV were analyzed.[13]

To estimate synchronization between 0.1-Hz rhythms in heart rate and microcirculation we used the method proposed by us recently.[16,22] At first we extracted LF components of RR-intervals and PPG using bandpass filtration (0.05–0.15 Hz). Then we determined the phases ϕ_1 and ϕ_2 of these

components using the Hilbert transform and calculated their difference $\phi = \phi_1 - \phi_2$. The presence of 1:1 phase synchronization is defined by the condition $|\phi| < \text{const}$.[22] In this case the phase difference $\varphi(t)$ fluctuates around a constant value. At last we detected all epochs of synchronization as the regions where φ fluctuates in time around a constant value, calculate their total duration S, and express it in percent of the duration T of the entire record:

$$S = \frac{\sum_{k=1}^{N} d_k}{T} \times 100\%$$

where d_k is the duration of the kth epochs of synchronization and N is the number of epochs. Index S defines the relative time of synchronization between the considered 0.1-Hz rhythms.

RESULTS

Overall, 5-year mortality among the post-AMI patients was 24 (19%). Cardiovascular events were the reason of death in 17 (71%) cases, in particular, recurrent MI in 16 (67%) cases and stroke in 1 (4%) case. In 6 (23%) cases the reason of sudden death was not clarified (pathologoanatomic study was not performed). Complication of attendant diseases was the reason of death in 1 (4%) case. Within the 5-year period of observation recurrent MI occurred in 29 (23%) patients.

We analyzed the choice of critical value of degree S of synchronization between 0.1-Hz rhythms, above which the quality of functional interaction between the regulatory LF processes in heart rate and microcirculation can be considered as satisfactory one in patients with AMI from the viewpoint of evaluation of personal fatal risk. Figure 1(A) displays a receiver operating characteristics (ROC) curve for different critical values of S at the second–fourth day after AMI with respect to evaluation of the risk of 5-year mortality. A ROC graph depicts relative trade-offs between benefits (true positives) and costs (false positives). An optimal point in ROC curve is the one that has high true positive rate plotted on the Y-axis and low false positive rate plotted on the X-axis. As the optimal relationship between sensitivity (Se) and specificity (Sp) of S as a factor of high risk of mortality we choose S = 20% with Se = 76% and Sp = 43% (1 – Sp = 57%, Fig. 1A).

Figure 1(B) shows a ROC curve for different critical values of S at the second–fourth day after AMI

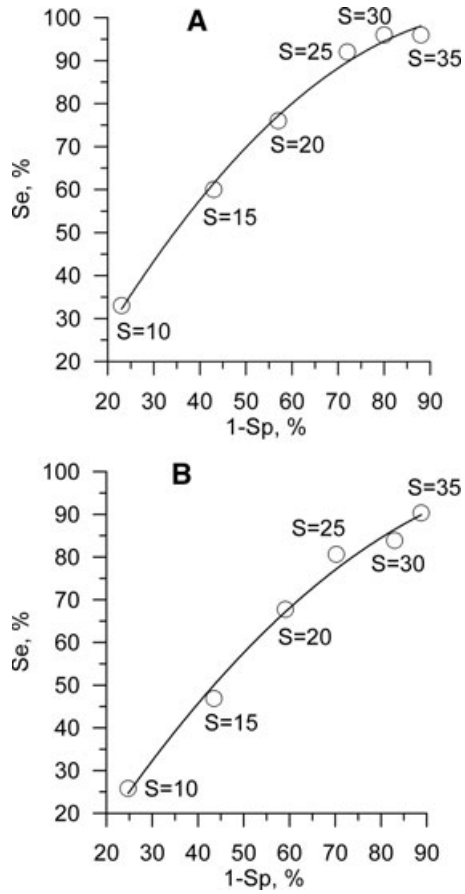

Figure 1. ROC curve for different critical values of index S at the second–fourth day after AMI. Se is sensitivity and Sp is specificity for evaluation of the 5-year risk of (A) mortality and (B) recurrent MI.

with respect to evaluation of the risk of recurrent MI. As the optimal relationship between sensitivity and specificity of S as a factor of high risk of recurrent MI we choose S = 20% with Se = 68% and Sp = 41% (1 – Sp = 59%, Fig. 1B).

The Kaplan–Meier cumulative curves are depicted in Figure 2(A) for subgroups of post-AMI patients with S < 20% and S ≥ 20% at the second–fourth day after AMI. The difference between these groups is statistically significant (P = 0.03). Probability of 5-year death was higher in patients with S < 20% at the second–fourth day after AMI compared with those with S ≥ 20% (23% vs 13%, P = 0.03). Kaplan-Meier estimates of cumulative probability of recurrent MI in subgroups of post-AMI patients with S < 20% and S ≥ 20% at the second–fourth day after AMI are shown in Figure 2(B). The intergroup difference is statistically significant

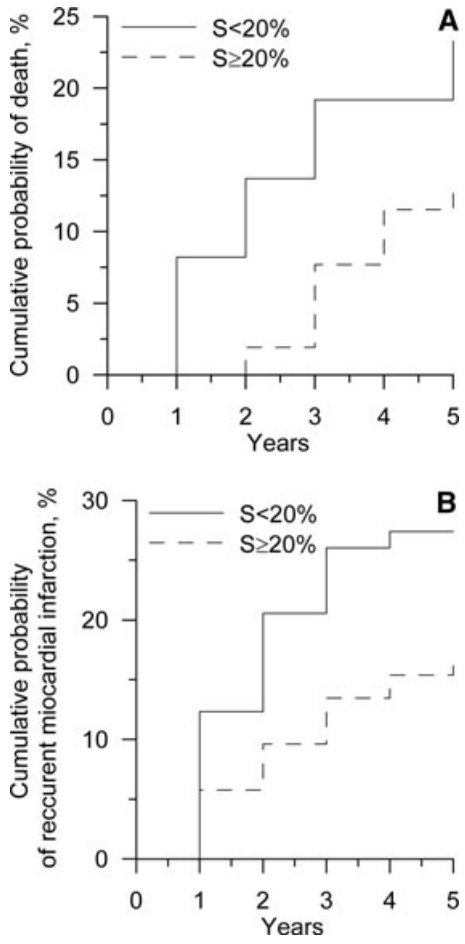

Figure 2. Kaplan–Meier estimates of cumulative probability of (A) death and (B) recurrent myocardial infarction, up to 5 years for subgroups of post-AMI patients with S < 20% and S ≥ 20% at the second–fourth day after AMI.

(P = 0.04). Probability of recurrent MI at 5 years was also higher in patients with S < 20% than those with S ≥ 20% at the second–fourth day after AMI (28% vs 17%, P = 0.04). Note that risks of death and recurrent MI differ across the considered subgroups of post-AMI patients beginning from the first year of observation.

Table 1 shows the baseline clinical and laboratory characteristics of post-AMI patients included in our study. Figure 3 illustrates the prognostic value of these baseline characteristics used for evaluation of the 5-year risk of mortality and recurrent MI in post-AMI patients. The results are presented as OR. We revealed that increased risk of 5-year mortality in post-AMI patients is associated with the following parameters: age over 65 years, stenocardia, prior MI, hypertension, stroke and temporary stroke in anamnesis, chronic obstructive disease of lungs, acute heart failure, dislipidemia (total cholesterol is greater than 190 mg/dL and/or triglycerides are greater than 100 mg/dL), left ventricular systolic dysfunction, taking diuretics, S < 20% at the second–fourth day after AMI, low power of LF and HF ranges of HRV power spectrum (Fig. 3A). Reduced risk of 5-year mortality was observed in post-AMI patients treated with statins and β-adrenoceptor blockers and by trombolysis in the presence of ST elevation in ECG.

As follows from Figure 3(B), the increased 5-year risk of recurrent MI in post-AMI patients is associated with the following characteristics: age over 65 years, male sex, prior MI, hypertension, stroke and temporary stroke in anamnesis, acute heart failure, left ventricular systolic dysfunction, S < 20% at the second–fourth day after AMI.

We analyze correlation between S values at the second–fourth day after AMI and other clinical characteristics (age, left ventricular ejection fraction, acute heart failure, and power of HRV spectrum in HF and LF ranges). It is found out that S shows weak correlation only with the power of HRV spectrum in LF range (r = 0.21, P = 0.02). The explanation of this observation is that the decrease of power of LF range of HRV power spectrum leads to deterioration of synchronization between 0.1-Hz oscillations in heart rate and PPG. However, deterioration of synchronization between the considered 0.1-Hz rhythms can be observed in the case of normal power of LF range of HRV power spectrum.

The correlation between S and other clinical characteristics was not significant. For example, the correlation between S and male sex and between S and the power of HRV spectrum in HF range was r = 0.17, P = 0.08 and r = 0.15, P = 0.12, respectively. The correlation coefficient r between S and other clinical factors was less than 0.1. The independence of S value on other clinical characteristics is additionally confirmed by multiple regression analysis ($R^2 = 0.13$, F = 0.59, P = 0.89).

We evaluated predictive value of abovementioned factors for the risk of mortality and recurrent MI in post-AMI patients using multivariable Cox's regression models. Table 2 shows the clinical characteristics used in the Cox's regression model for evaluation of the 5-year risk of mortality in patients after AMI. This model gives $\chi^2 = 51.8$

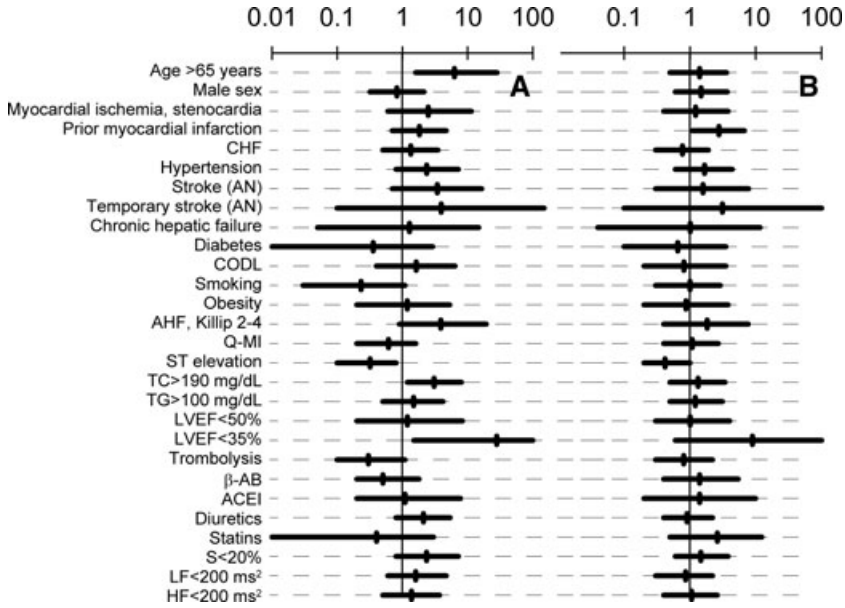

Figure 3. Evaluation of the 5-year risk of (A) mortality and (B) recurrent MI in patients with AMI in relation to clinical and laboratory characteristics. Probability of end point (death and MI) is shown as odds ratio (OR) together with its 95%-confidence interval for each parameter. The scale is logarithmic. CHF= chronic heart failure; AN = anamnesis; CODL = chronic obstructive disease of lungs; AHF = acute heart failure; TC = total cholesterol; TG = triglycerides; LVEF = left ventricular ejection fraction; β-AB = beta-adrenoceptor blockers; ACEI = angiotensin-converting enzyme inhibitors.

Table 2. Clinical Characteristics in the Cox's Regression Model for Evaluation of the 5-year Risk of Mortality in Patients after AMI

Parameter	Regression Coefficient β	Risk Index Exp(B)	Wald Test	Statistical Significance P
Acute heart failure, Killip	1.085	2.96	7.03	0.008
Index S	−0.092	0.91	4.35	0.016
Left ventricular ejection fraction	−0.081	0.93	4.01	0.037
Obesity	1.357	3.89	3.70	0.045
Temporary stroke	3.529	34.08	2.44	0.118
Age	0.072	1.07	2.24	0.134
Prior stroke	−1.255	0.28	0.82	0.178
Hypertension	1.335	3.80	1.71	0.191
Trombolysis	−0.976	0.38	1.37	0.242
Diabetes	−1.461	0.23	1.19	0.275
LF HRV	−0.001	0.99	1.18	0.277
HF HRV	0.001	1.00	1.19	0.278
Diuretics	0.776	2.17	0.97	0.324
ST elevation in ECG	−0.623	0.54	0.68	0.410
Stenocardia	0.810	2.25	0.47	0.493
Heart rate	−0.016	0.98	0.36	0.546
Beta-adrenoceptor blockers	0.468	1.60	0.23	0.63
Total cholesterol	−0.003	0.99	0.12	0.729
Male sex	−0.287	0.75	0.12	0.732
Prior MI	0.029	1.03	0.01	0.959

($P = 0.0001$). The values of the clinical characteristics in the model are summarized in Table 2.

Acute heart failure at AMI, $S < 20\%$ at the second–fourth day after AMI, left ventricular ejection fraction and obesity were identified as the most important factors for evaluation of the risk of 5-year mortality in patients after AMI ($\chi^2 = 14.2$, $P = 0.003$). The sign of regression coefficient β for these factors indicates that the risk of mortality in patients after AMI increases with the increase of acute heart failure Killip and obesity and the decrease of S and left ventricular ejection fraction. The risk index Exp(B) estimates the risk of 5-year mortality. It indicates that high Killip and obesity increase the risk of 5-year mortality in AMI patients in 3 and 3.9 times, respectively. According to the model the risk of death in AMI patients with high values of S and left ventricular ejection fraction is lower in about 0.9 times than in AMI patients with small values of S and left ventricular ejection fraction. Wald test gives the highest values for the four above-mentioned factors. Prognostic value of other clinical and laboratory characteristics exploited for assessment of the 5-year risk of mortality using Cox's regression models was not statistically significant ($P \geq 0.05$ for Wald test for each factor), Table 2.

To estimate the prognostic value of acute heart failure and S as the two most important factors for evaluation of the risk of 5-year mortality in patients after AMI we constructed additional Cox's regression model for two variables. This model shows that these two factors are in fact very important for evaluation of 5-year fatal risk ($\chi^2 = 10.5$, $P = 0.005$).

Figure 4 shows cumulative survival curves constructed using Cox's regression models for different S values at the second–fourth day after AMI for the cases of acute heart failure presence and absence. Probability of 5-year death was higher in patients with acute heart failure compared with those without it.

An informative content of the index S follows also from Figure 5. This figure shows the distribution functions of S values for the post-AMI patients who have died (Fig. 5A) and survived (Fig. 5B) within the 5-year period of observation. All the patients who have died during the study had $S \leq 27\%$ at the second–fourth day after AMI (Figure 5A). Moreover, 81% of these patients had $S < 20\%$.

As follows from Table 2, the index S and left ventricular ejection fraction entered in the considered

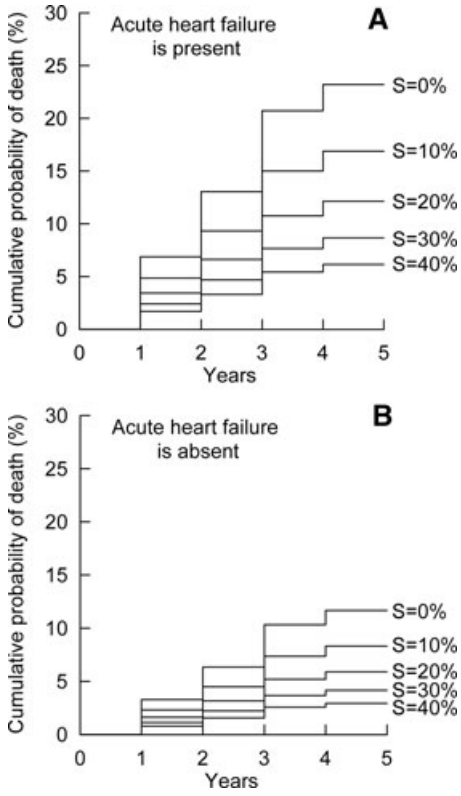

Figure 4. Estimation of cumulative probability of mortality in the group of post-AMI patients from the Cox's regression models constructed for different S values at the second–fourth day after AMI in (A) presence and (B) absence of acute heart failure.

multivariable Cox's model as a continuous variable show close prognostic values for the assessment of the 5-year fatal risk. To analyze the dependence between these two risk factors we plot Figure 6. As can be seen from Figure 6, S always takes values below 20% in the case of the pronounced left ventricular systolic dysfunction (ejection fraction is less than 35%). For greater values of ejection fraction the values of S have high dispersion. Besides, the patients with high values of ejection fraction could have small values of S.

It should be noted that comparing Cox's models with one variable we found out that the left ventricular ejection fraction below 35% entered in the model as a categorical variable has the highest prognostic value for evaluation of the 5-year risk of mortality in patients after AMI ($\chi^2 = 3.8$ and $P = 0.04$) in comparison with the other risk factors. However, in our study the case of pronounced left ventricular systolic dysfunction was rare in patients. In 92% of AMI patients in our study the

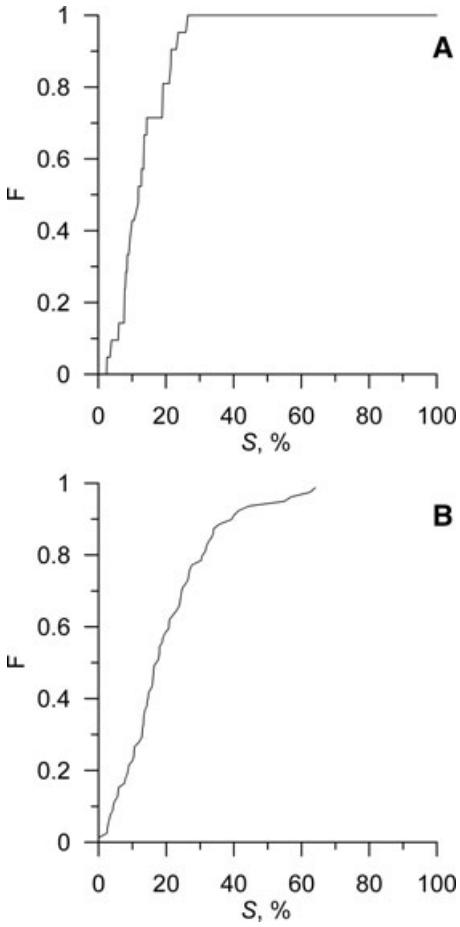

Figure 5. Distribution functions F of S values for the post-AMI patients who have died (A) and survived (B) within the 5-year period of observation.

ejection fraction was greater than 35% and in 75% of patients it was greater than 46%.

We used Cox's regression models for studying also the prognostic value of various clinical characteristics for evaluation of the 5-year risk of recurrent MI. These models reveal that prior MI is the most important factor for evaluation of the 5-year risk of recurrent MI in patients after AMI ($\chi^2 = 4.1$, $P = 0.03$). Combinations of above-mentioned clinical and laboratory characteristics including index S and power of LF and HF ranges of HRV power spectrum as risk factors for recurrent MI in post-AMI patients did not ensure a 0.05 significance level using Cox's regression models.

DISCUSSION

The results of the current prospective study demonstrate that degree S of synchronization between 0.1-Hz rhythms in heart rate and microcirculation is an important factor for evaluation of the risk of mortality in patients after AMI. Index S is exceeded in prognostic value only by acute heart failure. However, the prognostic value of index S is higher than that of established clinical characteristics, such as age over 65 years, stenocardia, prior MI, hypertension, stroke, chronic obstructive disease of lungs, low power of LF and HF ranges of HRV power spectrum, which increase the risk of mortality in patients after AMI.

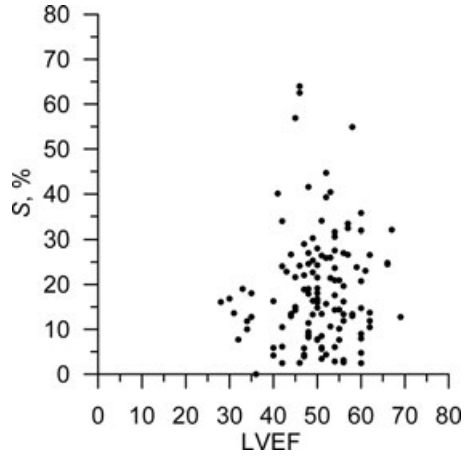

Figure 6. Dependence of index S on the left ventricular ejection fraction (LVEF).

Index S is a significant prognosticator for fatal cardiovascular events comparable to such important prognosticator as the left ventricular systolic dysfunction. Note that $S < 20\%$ exceeds the left ventricular ejection fraction in prognostic value in patients without pronounced left ventricular systolic dysfunction (ejection fraction is greater than 35%). As can be seen from Fig. 6, even the patients with normal values of ejection fraction such as 50–70% could have small values of S. Thus, the index S might provide significant clinical information that is not revealed by other risk factors.

The cutoff value $S = 20\%$ has been derived in our study from the present population. We have not checked the reproducibility of the results in different population. The cutoff values of index S should be tested in a prospective population.

High values of synchronization measure S for 0.1-Hz oscillations in heart rate and microcirculation that have been found for healthy subjects[16,22] indicate qualitative functional interaction between the mechanisms of regulation of heart rate and blood flow in skin microcirculation. Optimal

adjustment between the LF cardiovascular rhythms resulting in their comparatively high internal synchronization ensures a high adaptability of CVS. However, this synchronization may be deteriorated at AMI leading to a disruption of natural functional couplings within the system of CVS autonomic regulation. The results of the current study indicate that desynchronization of 0.1-Hz rhythms in CVS of post-AMI patients decreases the adaptation resources of CVS and significantly increases the risk of mortality.

It should be noted that another predictor of mortality after MI based on measuring the activity in LF band has been proposed.[24] Prevalent low-frequency oscillation (PLF) of heart rate was shown to be a potent risk predictor in post-MI patients.[24] However, in our study it was difficult to compare prognostic values of index S and PLF. To apply the method of PLF calculation one needs 10 or more 5-minute nonoverlapping segments of Holter recording. In our study we have only 10-minute records of ECG and PPG.

For evaluation of the 5-year risk of recurrent MI in post-AMI patients the prognostic value of index S is significantly lower than for evaluation of the risk of mortality. Nevertheless, this clinical characteristic may be included in the list of risk factors for recurrent MI (see Fig. 3B). Probably the autonomic dysfunction is not the leading initiating factor for pathogenesis of AMI, but it can be considered as a factor increasing its probability in the presence of other risk factors. For evaluation of the 5-year risk of recurrent MI the sensitivity and specificity of low S (<20%) at the first week after AMI were 68% and 41%, respectively.

CONCLUSION

In conclusion, the current study indicates that degree S of synchronization between 0.1-Hz rhythms in heart rate and microcirculation is an important prognostic factor for evaluation of the risk of cardiovascular events in patients after AMI. The value of S below 20% at the first week after AMI is a sensitive marker of high risk of mortality during the subsequent five years. We compared the prognostic value of the most important clinical factors for evaluation of the 5-year risk of mortality and recurrent MI in patients after AMI. Our study reveals that predictive value of index S for the risk of mortality in post-AMI patients is higher than that of most of established clinical characteristics.

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