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Synchronization of low-frequency oscillations in the cardiovascular system: Application to medical diagnostics and treatment

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Abstract. We investigate synchronization between the low-frequency oscillations of heart rate and blood pressure having in humans a basic frequency close to 0.1 Hz. A quantitative estimation of this synchronization based on calculation of relative time of phase synchronization of oscillations is proposed. We show that assessment of synchronization between the considered oscillations can be useful for selecting an optimal dose of beta-blocker treatment in patients after acute myocardial infarction. It is found out that low value of synchronization between the low-frequency rhythms in heart rate and blood pressure at the first week after acute myocardial infarction is a sensitive marker of high risk of mortality during the subsequent 5 years.

1 Introduction

Human cardiovascular system is one of the most important physiological systems whose operation is governed by several rhythmic processes interacting with each other. The most significant among them are the main heart rhythm, respiration, and low-frequency (LF) oscillations in heart rate (HR) and blood pressure (BP) with a basic frequency close to 0.1 Hz having a great importance for maintaining cardiovascular homeostasis [1,2]. The LF cardiovascular oscillations appear spontaneously across a frequency range from 0.04 Hz to 0.15 Hz, although generally close to 0.10 Hz. The origin of these oscillations is still a subject of controversy [3,4]. According to one hypothesis, the 0.1-Hz oscillations in HR and BP are largely an index of baroreflex gain [5,6]. On another hypothesis these oscillations have a central origin and represent an intrinsic property of autonomous neural network [7,8].

It has been found that LF cardiovascular oscillations can be synchronized with the main heart rhythm, respiration, and between themselves [9–11]. Optimal adjustment

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between these LF rhythmic processes resulting in their internal synchronization ensures a high adaptability of cardiovascular system that is necessary for global healthy behaviour of the organism. The analysis of synchronization of 0.1-Hz oscillations in HR and BP is based on the assumption that they are generated in different central neural structures involved in the autonomic regulation of cardiovascular system. Several facts count in favor of this hypothesis. In particular, the results of experiments where the LF oscillations were present only in one of the signals, either HR or BP, point to the presence of at least two different centers responsible for generation of oscillations with a frequency of about 0.1 Hz. For example, elimination of HR variability in supine humans by using a fixed-rate cardiac pacing with electrical stimuli did not alter LF BP oscillations [12]. On the other hand, implantation of a left ventricular assist device in patients with severe heart failure restore the LF oscillations in HR, even in the absence of any LF oscillations in BP [8]. After such implantation the native heart remains innervated and continues to be regulated by the autonomic nervous system while interactions between HR and BP are absent [8]. Another argument in favor of the hypothesis of the presence of two interacting self-sustained oscillators with basic frequencies close to 0.1 Hz is different response of the LF HR and BP oscillations to external stimulation [11].

In this paper we study synchronization between the LF oscillations in HR and BP in healthy subjects and patients after acute myocardial infarction (AMI). We discuss a possibility of controlling beta-blocker treatment in patients after AMI basing on a degree of synchronization between the 0.1-Hz oscillations in HR and BP. This degree of synchronization is used also for evaluation of the 5-year risk of mortality in patients after AMI.

2 Method of synchronization detection

To estimate synchronization between the LF cardiovascular oscillations we used the method proposed by us recently [11]. The signals of electrocardiogram (ECG) and photoplethysmogram (PPG) measured on the middle finger of the subject's hand were simultaneously recorded in a supine resting condition under spontaneous breathing. The signals were sampled at 250 Hz and digitized at 14 bits. The duration of each record was 10 minutes. Only ECG and PPG records without artifacts, extrasystoles, and considerable trends were left for the analysis.

Extracting from the ECG signal a sequence of RR intervals, i.e., a series of time intervals between the two successive R peaks, we obtain information about the HR variability. To obtain equidistant time series from not equidistant sequence of RR intervals we approximate it with cubic splines and resample with a frequency of 5 Hz.

Generally the Fourier power spectrum of RR intervals exhibits well-distinguished characteristic peaks at frequencies f_r and f_h associated with the respiratory and LF fluctuations of HR, respectively (Fig. 1(a)). A power spectrum of PPG signal exhibits peaks at frequencies f_r and f_p associated with the respiratory and LF oscillations of BP, respectively (Fig. 1(b)).

To extract the LF components of RR intervals and PPG signal we used band-pass 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 $\phi = \varphi_1 - \varphi_2$. The presence of 1:1 phase synchronization is defined by the condition $|\phi| < \text{const}$. In this case the phase difference $\phi(t)$ fluctuates around a constant value. We detected all epochs of synchronization as the regions where ϕ fluctuates in time around a constant value, calculated their total duration S, and expressed it in percent of the duration T of the entire record: $S = \left(\sum_{k=1}^{N} d_k/T\right) \times 100\%$, where d_k is the duration of the

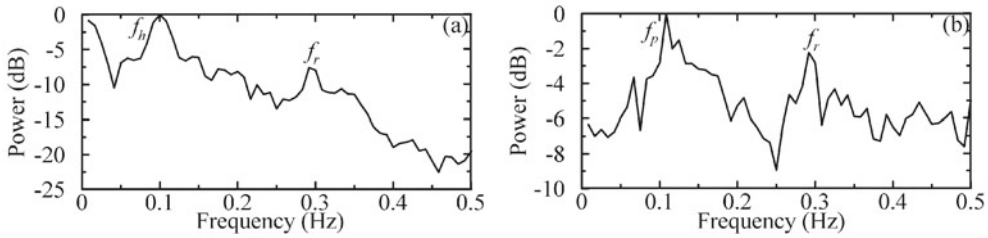

Fig. 1. Typical Fourier power spectra of RR intervals (a) and PPG signal (b). The frequencies f_r are associated with the respiratory oscillations and the frequencies f_h and f_p are associated with the LF oscillations.

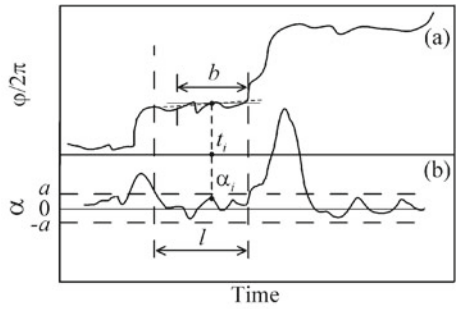

Fig. 2. Illustration of the automated procedure for detecting epochs of phase synchronization. (a) Linear approximation of normalized $\phi(t)$ in a moving window. (b) Slope of the approximating line.

k-th 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.

For automated detection of phase synchronization epochs we developed an algorithm based on a linear approximation of instantaneous phase difference $\phi(t)$ in a moving window. A time series of $\phi(t)$ normalized by 2π is linearly approximated in a window of width b by using the method of least squares (Fig. 2(a)). As a result, for a time moment t_i corresponding to the middle of the window we obtain a coefficient α_i of the approximating line slope (Fig. 2(b)). Moving the window by one point along the time series of $\phi(t)$, we calculate a slope α_{i+1} for a time moment t_{i+1}, and so on. In the regions of phase synchronization the relative phase $\phi(t)$ exhibits plateaus resulting in small values of $|\alpha|$. The regions of small $|\alpha|$ values are detected as synchronization episodes if $|\alpha| \leq |a|$, where a is a threshold value. Let us assume that the second necessary condition for the detection of synchronization is a sufficiently large duration of the region of small $|\alpha|$ values. The duration of this region should exceed the value l (Fig. 2(b)) to exclude short regions with a high probability of accidental coincidence of instantaneous phases of oscillations. It should be noted that finite width of the moving window does not allow us to investigate synchronization at the initial and final regions of $\phi(t)$ whose duration is equal to $b/2$. A similar method of automated detection of cardiorespiratory synchronization was used by Bartsch et al. [13]. However, it was based on the analysis of synchrograms instead of a relative phase.

We tested the method efficiency for detecting synchronization depending on the choice of the parameters b, a, and l. The value of S decreases with decreasing of $|a|$ or increasing of l. The dependence of S on the parameter b is not monotonous. Choosing

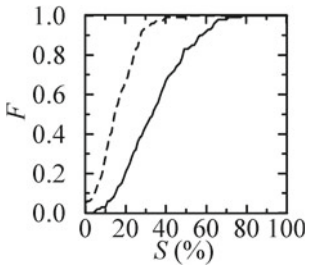

Fig. 3. Distribution functions of synchronization measure S in healthy subjects (solid line) and AMI patients (dashed line) calculated over all records.

the method parameters we were guided by the following concept: the automated procedure should identify the epochs of synchronization similarly to the usually used visual detection of synchronization. We found out that this condition is satisfied if l is about 1–2 characteristic periods of oscillations, b is close to the characteristic period, and $|a|$ is about 0.005–0.01. In this paper the following fixed values of the parameters: $b = 13\,\mathrm{s}$, $|a| = 0.01$, and $l = 16\,\mathrm{s}$ were used for the investigation of all experimental records.

3 Synchronization between LF cardiovascular oscillations in healthy subjects and patients after AMI

We studied 17 healthy subjects (8 women) aged 20–48 years and 42 patients (14 women) aged 41–80 years after AMI. With each subject several measurements were carried out at different days. In all, we measured 126 records for healthy subjects and 167 records for AMI subjects. For AMI patients all recordings were performed during the first three weeks after the infarction.

Using the proposed method we calculated the measure S of synchronization between the 0.1-Hz rhythms for all subjects. Figure 3 depicts the distribution functions of S values computed over all records of healthy subjects and AMI patients. We reveal that the measure S is greater in average in healthy subjects than in AMI patients. In our experiments S took the values 34.4±16.1% (mean ± standard deviation) for healthy individuals and $16.0 \pm 9.5\%$ for patients after AMI. It should be noted that the absolute values of S depend on the parameters of the automated procedure for synchronization detection considered in Sect. 2. However, in a wide range of these parameters variation the value of S remains in average considerably greater in healthy subjects than in AMI patients. We assume that the decrease of synchronization measure S in patients after AMI is caused by breakdown of functional couplings between the systems of LF regulation of HR and BP during infarction.

To investigate the changes in interaction between the LF cardiovascular rhythms during rehabilitation after the AMI we conducted supplementary measurements for the same patients but after 6 months after AMI. These subjects showed an increase of S in 1.3 times in average in comparison with their own S values during the first 3 weeks after AMI. However, these S values after 6 months after AMI were less in average in comparison with average S values in healthy subjects.

The evidence that substantial decrease of phase synchronization index S between the LF cardiovascular rhythms in the group of AMI patients is caused by infarction rather than effects of aging is substantiated by the following two observations. Firstly, at a spontaneous breathing the variability of the phase shift between HR and BP fluctuation near the frequency of 0.1 Hz is similar in young versus older healthy subjects

[14]. Secondly, as we have observed, the subjects after 6 months after AMI show in average an increase of S in comparison with themselves during the first 3 weeks after AMI. This observation suggests that the functional couplings in the autonomic control system of the cardiovascular system leading to synchronization of 0.1-Hz oscillations may be gradually restored after AMI.

4 Control of treatment of patients after AMI basing on the degree of synchronization between LF cardiovascular oscillations

The analysis of synchronization between the LF oscillations in HR and BP seems to be promising for studying a degree of disruption of autonomic regulation of the cardiovascular system and for controlling the efficiency of medical treatment and rehabilitation in patients after AMI. Such patients are usually treated with beta-blockers that improve autonomic function and decrease fatal risk. In accordance with the contemporary guidelines for beta-blocker treatment, the target dose should be used or, if not tolerated, the highest tolerated dose [15]. At present time the control of beta-blocker treatment is based mainly on the analysis of HR, ejection fraction, and BP. However, there is no any criterion for controlling beta-blocker treatment basing on the functional state of cardiovascular system and interaction between its subsystems. The aim of our study was to propose a criterion for selecting an optimal dose of beta-blocker in AMI patients basing on the degree of synchronization between 0.1-Hz oscillations in HR and BP.

Our study included 37 patients with coronary heart disease (16 women) aged between 41 and 77 years with AMI six months prior to the start of the study. We used the following criteria to enroll the patients in our study:

i) the confirmed diagnosis of AMI [16] about six months prior to the start of the study;
ii) the absence of systolic dysfunction of left ventricular (ejection fraction is greater than 50%);
iii) everyday treatment with beta-blockers in doses no more equivalent of metoprolol 50 mg/day.

The exclusion of patients with small values of ejection fraction from the study allowed us to reduce the influence of chronic heart failure on the results of investigation of changes in synchronization index S in response to beta-blocker treatment.

We studied relative changes in degree S of synchronization between 0.1-Hz rhythms in RR intervals and PPG as a response to vertical tilt before and after three-month treatment with the highest tolerated dose of beta-blocker (metoprolol), which was selected for each patient using titration. We have tested the synchronization measure S by calculating it for the same subject several times per day and within several days. The obtained results show that S takes very close values for the data recorded within one or next day. The tilt test protocol was the following:

i) subject was lying in a horizontal position. It was a preliminary stage lasting 10 minutes without signal recording;
ii) the signals were recorded within 10 minutes in the horizontal position of patient's body;
iii) subject was put in a vertical position with a tilt angle of about 80°. To exclude the transients the signals were not registered within 5 minutes;
iv) the signals were recorded within 10 minutes in the vertical position of patient's body.

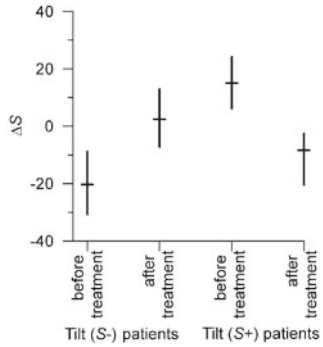

Fig. 4. Change in S as a response to vertical tilt in Tilt (S-) and Tilt ($S+$) AMI patients before and after three-month metoprolol treatment with the highest tolerated dose. Medians with inter-quartile ranges (25%, 75%) are shown.

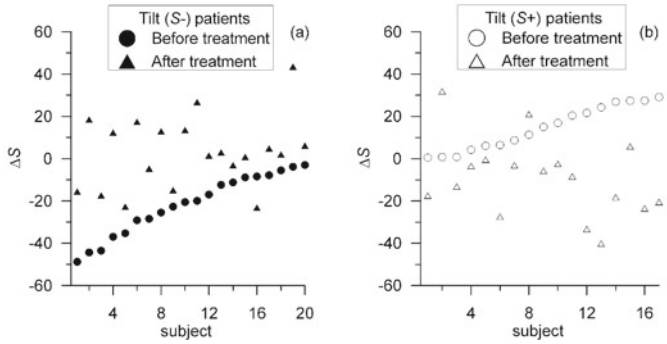

Fig. 5. Individual ΔS values for Tilt (S-) and Tilt ($S+$) AMI patients before and after three-month metoprolol treatment with the highest tolerated dose. The subjects are ordered with respect to ΔS value at the beginning of the study.

We calculated $\Delta S = S_v - S_h$, where S_v is the degree of synchronization between 0.1-Hz rhythms in the vertical position and S_h is the degree of synchronization in the horizontal position. Two groups of patients were identified on the basis of the results. The first group was composed of patients ($n = 20$) with negative ΔS ($P = 0.003$) at the beginning of the study (Fig. 4). We named this group as Tilt (S-) patients. The second group was composed of patients ($n = 17$) with positive ΔS ($P = 0.002$) before treatment with the highest tolerated metoprolol dose (Fig. 4). This group was named as Tilt ($S+$) patients. After three-month treatment with the highest tolerated metoprolol dose S increased as a response to vertical tilt in Tilt (S-) patients ($P = 0.04$) and decreased in Tilt ($S+$) patients ($P = 0.03$) (Fig. 4).

To illustrate individual changes in ΔS we plot the figure that shows individual ΔS values for subjects from the groups of Tilt (S-) and Tilt ($S+$) AMI patients at the beginning of the study and after three-month treatment with the highest tolerated metoprolol dose (Fig. 5).

Table 1 shows estimated S values in two groups of patients before and after three-month metoprolol treatment. As can be seen from the table, before metoprolol treatment S values in vertical position were greater in Tilt ($S+$) patients than in Tilt (S-) patients. Since S increases as a response to vertical tilt in healthy subjects, the response to a tilt test in Tilt (S-) patients was postulated to indicate the need to increase beta-blocker dose for correction of autonomic dysfunction of cardiovascular

Table 1. Estimated S values in Tilt (S-) and Tilt (S+) AMI patients before and after three-month metoprolol treatment with the highest tolerated dose. The data are shown as medians with inter-quartile (25%, 75%) ranges. Sign * indicates a significant difference ($P < 0.05$) from parameter values before metoprolol treatment. Sign + indicates a significant difference ($P < 0.05$) from the same parameter in Tilt (S-) patients.

	Tilt (S-) patients		**Tilt (S +) patients**	
Parameter	**before treatment**	**after treatment**	**before treatment**	**after treatment**
S_h, %	41 (29, 48)	27 (22, 41)*	26 (19, 29)$^+$	37 (27, 43)*$^+$
S_v, %	19 (11, 25)	32 (25, 37)*	37 (33, 43)$^+$	24 (19, 33)*$^+$

system. On the contrary, the response to a tilt test in Tilt (S+) patients was postulated to indicate an already adequate beta-blocker dose. Otherwise, the increase of beta-blocker dose for this group of patients will increase autonomic dysfunction of cardiovascular system. Indeed, after three-month metoprolol treatment Tilt (S-) and Tilt (S+) patients show opposite changes in S in response to a tilt test. The dynamics of changes in S was positive in Tilt (S-) patients and negative in Tilt (S+) patients.

The results of our study show that assessment of synchronization of 0.1-Hz HR and BP oscillations as a response to a tilt test can possibly be used as a guideline for selecting optimal beta-blocker dose in post myocardial infarction patients. Otherwise, the pay for decrease of angina pectoris events under the treatment with the highest tolerated metoprolol dose will be the decrease in S in Tilt (S+) patients. As we have shown recently (see Sect. 5), the decrease in S is the major factor of fatal risk in AMI patients. Thus, the prescription of high doses of beta-blocker to subjects with increased S as a response to vertical tilt after six months after AMI (about 46% of patients in our study) should be probably avoided or done with care, since it increases autonomic dysfunction of cardiovascular system.

5 Evaluation of the five-year risk of mortality in patients after AMI using degree of synchronization of LF cardiovascular oscillations

We have shown above that synchronization between the 0.1-Hz oscillations in HR and BP is deteriorated at AMI and the values S of synchronization between these oscillations can be used for estimating a degree of disruption of autonomic regulation of the cardiovascular system. Taking into account this observation we compared the prognostic value of synchronization measure S and established clinical characteristics for evaluation of the five-year risk of mortality in patients after AMI. Our study included 125 patients after AMI (53 women) aged between 30 and 83 years. The period of observation of patients was 5 years with checkpoints at the second-fourth day after infarction and after each year after infarction. Death was defined as endpoint of observation.

We analysed the choice of critical value of S, above which the quality of functional interaction between the regulatory LF processes in HR and BP can be considered as satisfactory one in patients with AMI from the viewpoint of evaluation of personal fatal risk. Figure 6 displays a receiver operating characteristics (ROC) curve for different critical values of S at the second-fourth day after infarction with respect to evaluation of the risk of five-year mortality. A ROC graph depicts relative tradeoffs 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

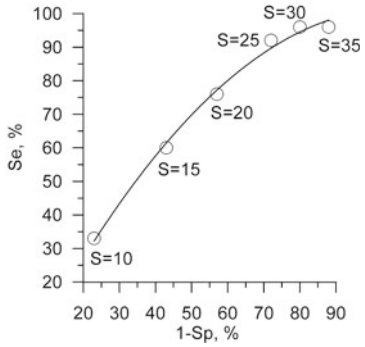

Fig. 6. ROC curve for different critical values of index S at the second-fourth day after AMI. Se is sensitivity and Sp is specificity for evaluation of the five-year risk of mortality.

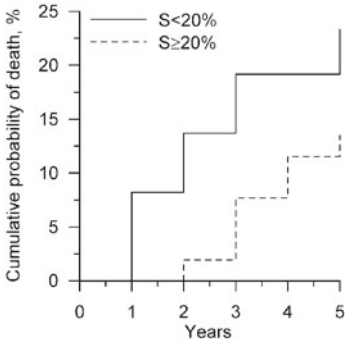

Fig. 7. Kaplan-Meier estimates of cumulative probability of death up to 5 years for subgroups of post-AMI patients with $S < 20\%$ and $S \geq 20\%$ at the second-fourth day after AMI.

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 $S = 20\%$.

The Kaplan–Meier cumulative curves are depicted in Fig. 7 for subgroups of patients with $S < 20\%$ and $S \geq 20\%$ at the second-fourth day after AMI. The difference between these groups is statistically significant ($P = 0.03$). Probability of five-year death was higher in patients with $S < 20\%$ at the second-fourth day after infarction compared with those with $S \geq 20\%$. Note that risk of death differs across the considered subgroups of patients beginning from the first year of observation.

We compared predictive value of baseline clinical characteristics for evaluation of the five-year risk of mortality in patients after AMI using multivariable Cox's regression model. Acute heart failure at myocardial infarction, $S < 20\%$ at the second-fourth day after infarction, left ventricular ejection fraction and obesity were identified as the most important factors for evaluation of the risk of five-year mortality in patients after AMI ($\chi^2 = 14.2$, $P = 0.003$). The risk of mortality in patients increases with the increase of acute heart failure Killip and obesity and the decrease of S and left ventricular ejection fraction. 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, hypertension, stenocardia, prior myocardial infarction, stroke, chronic obstructive disease of lungs, low power of LF and high-frequency ranges of HR variability power spectrum, which increase the risk of mortality in patients after AMI.

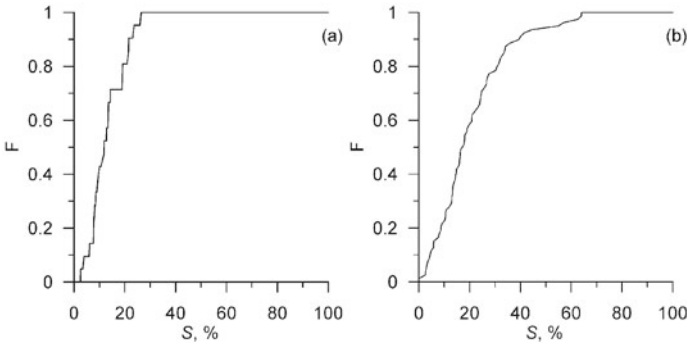

Fig. 8. Distribution functions F of S values for the post AMI patients who have died (a) and survived (b) within the five-year period of observation.

We analysed correlation between S values at the second-fourth day after myocardial infarction and other clinical characteristics. It is found out that S shows weak correlation only with the power of HR variability spectrum in the LF range ($r = 0.21$, $P = 0.02$). The correlation between S and other clinical characteristics was not significant.

It should be noted that left ventricular ejection fraction entered in the multivariable Cox's regression model as a continuous variable yields in prognostic values for the assessment of the five-year fatal risk only to acute heart failure and index S. However, 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 five-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 patients in our study the ejection fraction was greater than 35%.

An informative content of the index S follows also from Fig. 8. It shows the distribution functions of S values for the post AMI patients who have died (Fig. 8(a)) and survived (Fig. 8(b)) within the five-year period of observation. All the patients who have died during the study had $S \leq 27\%$ at the second-fourth day after AMI (Fig. 8(a)). Moreover, 81% of these patients had $S < 20\%$.

The results of the our study indicate that desynchronization of 0.1-Hz rhythms in cardiovascular system of post AMI patients decreases the adaptation resources of cardiovascular system and significantly increases the risk of mortality. Degree S of synchronization between the 0.1-Hz rhythms in HR and BP is an important prognostic factor for evaluation of the risk of fatal events in patients after AMI. The value of S below 20% at the first week after infarction is a sensitive marker of high risk of mortality during the subsequent 5 years. The predictive value of index S for the risk of mortality in post myocardial infarction patients is higher than that of most of established clinical characteristics.

6 Conclusion

We have investigated synchronization between the LF oscillations in HR and BP having in humans a basic frequency close to 0.1 Hz. For quantitative estimation of synchronization between these processes we used the method based on calculation of the measure S of phase synchronization of oscillations. This method is based on a linear approximation of instantaneous phase difference of analyzed signals in a moving

window. It is found out that healthy subjects exhibit in average substantially longer epochs of synchronization between the LF cardiovascular rhythms than patients after AMI.

We assume that assessment of synchronization of 0.1-Hz HR and BP oscillations, as a response to a tilt test can possibly be useful for selecting an optimal dose of beta-blocker treatment in patients after AMI. Two groups of AMI patients were identified. The first group was composed of patients with decreased S as a response to vertical tilt at the beginning of the study. The patients with increased S during vertical tilt before treatment with the highest tolerated beta-blocker dose were attributed to the second group. The response to vertical tilt in the first group of patients was postulated to indicate the need to increase beta-blocker dose, and in turn, the response in the second group to indicate an already adequate beta-blocker dose.

We have shown that low value of synchronization ($S < 20\%$) between the 0.1-Hz rhythms in HR and BP at the first week after AMI is a sensitive marker of high risk of mortality during the subsequent 5 years. Our study revealed 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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