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Synchronization of 0.1 Hz Oscillations in Heart Rate and Blood Pressure: Application to Treatment of Myocardial Infarction Patients

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***Abstract*—**Synchronization between 0.1 Hz oscillations in heart rate and blood pressure is studied and its change during vertical tilt is evaluated in 37 myocardial infarction patients. Two groups of patients are identified with decreased and increased, respectively, synchronization of the studied oscillations as a response to a tilt test. It is shown that assessment of synchronization of 0.1 Hz oscillations as a response to vertical tilt can be used as a guideline for selecting optimal dose of beta-blocker treatment in post-myocardial infarction patients.

***Keywords*—**Cardiovascular system, heart rate variability, synchronization.

I. Introduction

BETA-BLOCKERS play an important role in complex treatment in myocardial infarction (MI) patients with coronary heart disease (CHD) [1]. At present time the control of beta-blocker treatment is based mainly on the analysis of heart characteristics such as heart rate (HR), ejection fraction and blood pressure (BP). However, there is no any criterion for controlling beta-blocker treatment basing on the functional state of cardiovascular system (CVS) and interaction between its subsystems.

Heart rate variability (HRV) is a well-known marker of autonomic dysfunction in post-MI patients with CHD [2]. Along with classical methods of HRV evaluation different nonlinear methods are used in recent years in clinical practice for studying autonomic regulation of CVS. It is known that operation of CVS is governed by several rhythmic processes interacting with each other [3], [4]. Among them are the rhythms with a basic frequency close to 0.1 Hz observed in HRV and arterial pressure [3], [4]. The origin of these low-frequency oscillations is still a subject of controversy. According to one hypothesis, these 0.1 Hz oscillations have a central origin [5], [6]. On another hypothesis they are largely an index of baroreflex gain [7], [8].

It has been found that 0.1 Hz cardiovascular oscillations can be synchronized between themselves [9], [10] for ensuring a high adaptability of CVS. However, this synchronization is deteriorated at MI leading to disruption of natural functional couplings within the system of CVS autonomic regulation [9], [10]. Peculiarities of synchronization between the rhythms of CVS reflect its state [11], [12] and may contain useful information for medical diagnostics. It is important to study the influence of cardioselective beta-blockers on autonomic regulation of CVS in post-MI patients with CHD.

The aim of this study was to propose a criterion for selecting an optimal dose of cardioselective beta-blocker (metoprolol) in MI patients basing on changes in synchronization between 0.1 Hz oscillations in HR and BP.

II. Methods

A. Study Setting and Patient Selection

The study was approved by the institutional ethical board and informed consent was obtained from all participants. Our study included 37 patients with CHD (18 (49%) females and 19 (51%) males) aged between 41 and 77 years with acute MI six months prior to the start of the study. Before inclusion into this study all patients were treated in accordance with contemporary recommendations for acute coronary syndrome treatment (beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and other drugs) within 6 months after acute MI. It should be noted that all these patients were treated with cardioselective beta-blocker before the study in doses no more equivalent of metoprolol 50 mg/day.

To examine autonomic control of CVS we carried out spectral analysis of HRV and estimated degree of synchronization between 0.1 Hz rhythms in HR and BP. Electrocardiogram (ECG), photoplethysmogram (PPG)

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measured on the middle finger of the subject's hand, and respiration were simultaneously recorded during a tilt test before and after three-month treatment with maximal tolerated metoprolol dose. The signals were recorded between 13 and 15 hours under spontaneous breathing. The duration of all records was 10 minutes both for horizontal and vertical position of patient's body during the tilt test. All signals were sampled at 250 Hz and digitized at 14 bits.

Extracting from the ECG signal a sequence of R-R intervals one can obtain information about HRV. To obtain equidistant time series from not equidistant sequence of R-R intervals this sequence was approximated with cubic splines and resampled with a frequency of 5 Hz.

The record of respiration was used to control evenness of breathing. The time series with forced inspiration and delays in breathing were excluded from the analysis. For further analysis only ECG and PPG records without artifacts, extrasystoles and considerable trends were left.

The maximal tolerated metoprolol dose was selected for each MI patient using titration and taking into account the patient HR and arterial pressure. The metoprolol dose was selected to be 200 mg/day for 30 (81%) patients and 100 mg/day for 7 (19%) patients.

B. Statistical Analysis

The Shapiro–Wilk test was applied to check whether the HRV spectral data are approximately normally distributed. Since these data occur to be non-normal, their further analysis was carried out using non-parametric statistical methods. To compare the variables the Mann–Whitney test was used. Continuous variables are reported as medians (Me) with inter-quartile ranges (25%, 75%). Categorical data are presented as frequencies and percentages. The obtained estimations were considered statistically significance if $P < 0.05$.

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 low-frequency (LF) range, 0.04–0.15 Hz, of HRV were analysed [13].

C. Method of Detection of Phase Synchronization

To estimate synchronization between 0.1 Hz rhythms in HR and BP we used the following method. At first LF components of R-R intervals and PPG were extracted using bandpass filtration (0.05–0.15 Hz). To calculate the phase of LF oscillations of HR the analytic signal $\zeta(t)$ [14] is constructed for the signal $s(t)$ obtained as a result of bandpass filtration of R-R intervals. The signal $\zeta(t)$ is a complex function of time defined as

$$\zeta(t) = s(t) + i\tilde{s}(t) = A(t)\exp\left(i\phi(t)\right), \tag{1}$$

where $A(t)$ and $\phi(t)$ are respectively the amplitude and the phase of the analytic signal, and function $\tilde{s}(t)$ is the Hilbert transform of $s(t)$,

$$\tilde{s}(t) = \frac{1}{\pi}\text{P.V.}\int_{-\infty}^{+\infty}\frac{s(\tau)}{t-\tau}d\tau, \tag{2}$$

where P.V. means that the integral is taken in the sense of the Cauchy principal value. Phase $\phi(t)$ is defined from (1) as

$$\phi(t) = \arctan\left(\tilde{s}(t)/s(t)\right). \tag{3}$$

In a similar way the phase of LF oscillations of BP is calculated from the filtered signal of PPG.

To detect synchronization between the slow oscillations of BP pressure and HR the phase difference

$$\varphi = \phi_p - \phi_h \tag{4}$$

is calculated, where ϕ_p is the phase of LF oscillations of BP and ϕ_h is the phase of LF oscillations of HR. The presence of 1:1 phase synchronization is defined by the condition $|\varphi| < \text{const}$. In this case the phase difference $\varphi(t)$ fluctuates around a constant value as in Fig. 1(a).

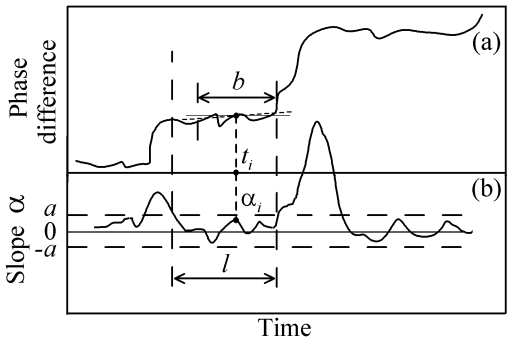


Fig. 1 Illustration of the automated procedure for detecting epochs of phase synchronization. (a) Linear approximation of normalized $\varphi(t)$ in a moving window. (b) Slope of the approximating line

After detection of all epochs of synchronization in the plot of $\varphi(t)$ their total duration is calculated and expressed in percent of the duration of the entire record. The obtained measure S is named as the total percent of phase synchronization.

For automated detection of phase synchronization epochs we used an algorithm developed by us recently [9], [10], which is based on a linear approximation of instantaneous phase difference $\varphi(t)$ in a moving window. A time series of $\varphi(t)$ normalized by 2π is linearly approximated in a window of width b by using the method of least squares [Fig. 1(a)]. As a result, for a time moment t_i corresponding to the middle of the window a coefficient α_i of the approximating line slope is obtained [Fig. 1(b)]. Moving the window by one point along the time series of $\varphi(t)$, one can calculate a slope α_{i+1} for a time moment t_{i+1}, and so on. In the regions of phase

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synchronization the relative phase $\varphi(t)$ exhibits plateaus resulting in small values of $|\alpha|$. The regions of small $|\alpha|$ values are detected as synchronization episodes if $|\alpha| \le |a|$, where a is a threshold value. A sufficiently large duration of the region of small $|\alpha|$ values is used as the second necessary condition for the detection of synchronization. The duration of this region should exceed the value l [Fig. 1(b)] to exclude short regions with a high probability of accidental coincidence of instantaneous phases of oscillations.

The method efficiency for detecting synchronization was tested depending on the choice of the parameters b, a, and l. The total percent of phase synchronization decreases with decreasing of $|a|$ or increasing of l. The dependence of S on the parameter b is not monotonous. The choice of the method parameters was based on the following concept: the automated procedure should identify the epochs of synchronization similarly to the usually used visual detection of synchronization and ensure a statistical significance of the results. It was found that these conditions are 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: $b = 13$ s, $|a| = 0.01$, and $l = 16$ s were used for the investigation of all experimental records.

We tested the proposed 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.

III. Results

After three-month treatment with maximal tolerated metoprolol dose the number of angina pectoris events in MI patients decreased from 24 ± 3 to 10 ± 7 per week ($P = 0.01$). This result testifies the clinical efficiency of metoprolol treatment in post-MI patients with CHD. The change in values of BP was not statistically significant in all patients during our study.

Relative changes in degree S of synchronization between 0.1 Hz rhythms in HR and BP as a response to vertical tilt were studied before and after three-month treatment with maximal tolerated dose of metoprolol. 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 the MI 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. 2). This group was named as Tilt (S-) patients. The second group was composed of patients ($n = 17$) with positive ΔS ($P = 0.002$) before treatment with maximal tolerated metoprolol dose (Fig. 2). This group was named as Tilt (S+) patients.

After three-month treatment with maximal 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. 2).

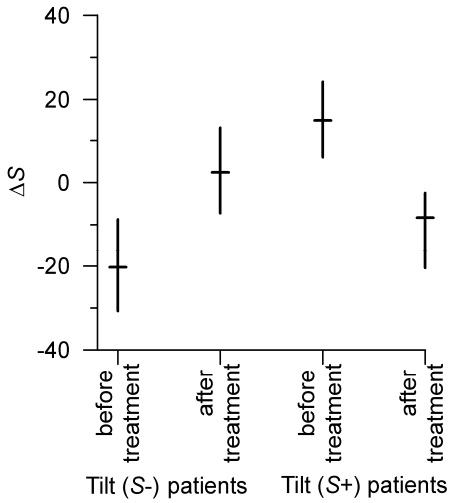


Fig. 2 Change in S as a response to vertical tilt in Tilt (S-) and Tilt (S+) MI patients before and after three-month metoprolol treatment with maximal tolerated dose. Medians with inter-quartile ranges (25%, 75%) are shown

Note that before metoprolol treatment S values in MI patients in vertical position were significantly greater in Tilt (S+) patients than in Tilt (S-) patients ($P = 0.006$) (Table I).

TABLE I
Estimated S and HRV Parameters in Tilt (S-) and Tilt (S+) MI Patients before and after Three-Month Metoprolol Treatment with Maximal Tolerated Dose

Parameter and body's position		Tilt (S-) patients (n=20)		Tilt (S+) patients (n=17)	
		before treatment	after treatment	before treatment	after treatment
S (%)	h	41 (29, 48)	27 (22, 41)*	26 (19, 29)$^+$	37 (27, 43)*$^+$
	v	19 (11, 25)	32 (25, 37)*	37 (33, 43)$^+$	24 (19, 33)*$^+$
HR (s^{-1})	h	73 (60, 81)	66 (55, 74)*	71 (66, 78)	68 (59, 73)*
	v	80 (69, 88)	72 (59, 80)*	83 (75, 89)	75 (64, 81)*
LF (ms^2)	h	87 (48, 147)	114 (58, 192)	145 (60, 260)$^+$	208 (74, 435)*$^+$
	v	99 (36, 321)	66 (41, 122)	138 (54, 167)	96 (59, 262)$^+$
HF (ms^2)	h	151 (65, 257)	170 (90, 218)	107 (55, 299)	178 (68, 378)
	v	92 (34, 163)	76 (34, 160)	47 (26, 110)$^+$	102 (24, 232)$^+$

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After three-month metoprolol treatment with maximal tolerated dose S values in vertical position became significantly greater in Tilt (S-) patients than in Tilt (S+) patients ($P = 0.02$) (Table I). In Table I the data are shown as Me (25%, 75%). The horizontal and vertical body's position are noted as h and v, respectively. The symbol * indicates significant difference ($P < 0.05$) from parameter values before metoprolol treatment. The symbol + indicates significant difference ($P < 0.05$) from the same parameter in Tilt (S-) patients.

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+) MI patients at the beginning of the study and after three-month treatment with maximal tolerated metoprolol dose (Fig. 3).

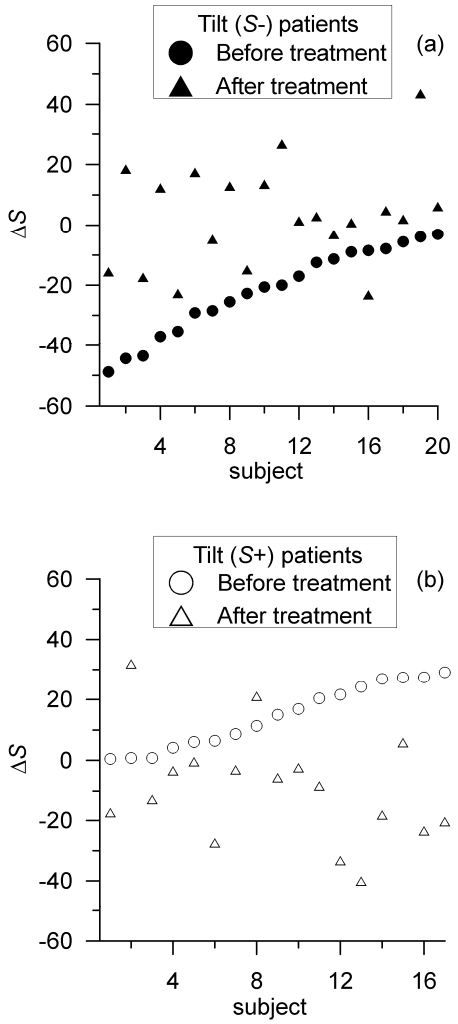


Fig. 3 Individual ΔS values for Tilt (S-) and Tilt (S+) MI patients before and after three-month metoprolol treatment with maximal tolerated dose. The subjects are ordered with respect to ΔS value at the beginning of the study

After metoprolol treatment a decrease of HR was observed in both groups of patients (Table I). The power of LF band in HRV spectrum was greater in Tilt (S+) patients in comparison with Tilt (S-) patients ($P = 0.01$) both before and after metoprolol treatment. The power of HF band in HRV spectrum was lower in Tilt (S+) patients than in Tilt (S-) patients ($P = 0.04$). After three-month metoprolol treatment the HF band power became greater in Tilt (S+) patients than in Tilt (S-) patients ($P = 0.05$) (Table I).

Dependence of S on the power of HRV spectrum in LF and HF bands was not revealed for both groups of patients. Coefficient R^2 in multiple regression equations took the values from 0.027 to 0.36 ($P > 0.05$) for different combinations of investigated parameters.

IV. Discussion

A typical medical mistake at beta-blocker treatment in MI patients is the use of small doses of these drugs. On the other hand, the increase of beta-blocker dose up to maximal tolerated one is not always justified. The number of angina pectoris events decreases with the increase of beta-blocker dose. However, the results of our study show that increase of beta-blocker dose has no effect on BP dynamics.

It is revealed that after three-month metoprolol treatment Tilt (S-) and Tilt (S+) post-MI patients with CHD show opposite changes in S in response to a tilt test. This observation is explained probably by different features of CVS autonomic regulation in these two groups. Since S increases as a response to vertical tilt in healthy subjects [9], [15], the response in Tilt (S-) patients was postulated to indicate the need to increase beta-blocker dose for correction of autonomic dysfunction of CVS. On the contrary, the response 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 CVS.

Probably, the revealed distinctions between the groups of MI patients are caused by cardioselectivity of metoprolol influence on β_1-type adrenoreceptors. Blocking of β_1-type adrenoreceptors modulates the activity of heart autonomic regulation mechanisms at 0.1 Hz owing to the changes of feedback loop features. The activity of the efferent part of feedback loop reduces leading to the changes in the properties of information flow from heart to central structure of CVS regulation.

After three-month treatment with maximal tolerated metoprolol dose the Tilt (S-) MI patients had significantly lower power of LF band in HRV spectrum than Tilt (S+) patients. It means that activity of autonomic regulation of heart at 0.1 Hz is lower in Tilt (S-) patients than in Tilt (S+) patients. The increase of beta-blocker dose in Tilt (S-) patients increases the activity of heart autonomic regulation. As the result, the normal interaction between mechanisms of HR and BP regulation can be restored leading to increase of S values. In Tilt (S+) patients the LF band power is higher than that in Tilt (S-) patients. The activity of heart autonomic regulation at 0.1 Hz is also high in Tilt (S+) patients. Thus, the increase of

beta-blocker dose will result in decrease of *S*.

In Fig. 4 the dependence of ΔS on the value of *S* in horizontal position is plotted for each group of MI patients before and after metoprolol treatment.

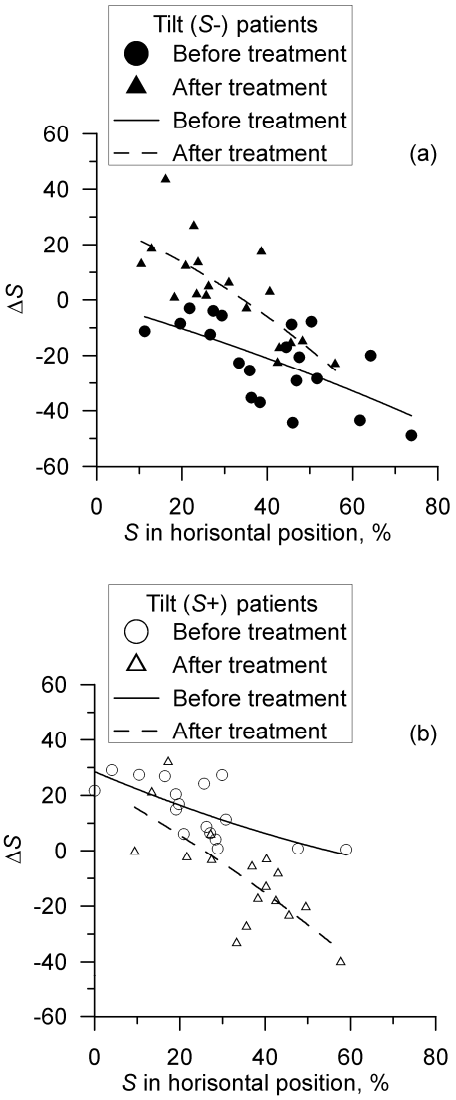


Fig. 4 Approximation curves for dependence of ΔS on *S* in horizontal position before and after three-month metoprolol treatment with maximal tolerated dose in Tilt (*S*-) and Tilt (*S*+) MI patients

As can be seen from Fig. 4, after metoprolol treatment with maximal tolerated dose the approximation curve shifts up in Tilt (*S*-) MI patients and below in Tilt (*S*+) MI patients. The three-month metoprolol treatment results in an increase in ΔS by 5% or more in Tilt (*S*-) patients and a decrease in ΔS by 5% or more 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-MI patients. Otherwise, the pay for decrease of angina pectoris events under the treatment with maximal tolerated metoprolol dose will be the decrease in *S* in Tilt (*S*+) patients. As it was shown recently, the decrease in *S* is the major factor of fatal risk in post-MI patients [16].

Our study has limitations. The patients with abnormalities in HR impeding the analysis of HRV were excluded from our study. The patients with pronounced abnormalities in BP were also excluded from the study. The reason is that the records from such patients are not suitable for the analysis of phase synchronization between the considered cardiovascular rhythms. The number of such subjects was 4 (10%).

V. Conclusion

In our study the criterion for selecting an optimal dose of beta-blocker treatment in post-MI patients with CHD is proposed basing on changes in synchronization between 0.1 Hz oscillations in HR and BP. It is revealed that MI patients with increased *S* as a response to vertical tilt before the treatment period with maximal tolerated beta-blocker dose (46% of all post-MI patients) do not need the increase of beta-blocker dose.

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