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Selection of optimal dose of beta-blocker treatment in myocardial infarction patients based on changes in synchronization between 0.1 Hz oscillations in heart rate and peripheral microcirculation

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Background **Selection of the optimal dose of beta-blocker treatment in myocardial infarction (MI) patients is problematic because of a lack of well-established guidelines.**

Methods **We evaluated changes in synchronization between 0.1 Hz oscillations in heart rate (HR) and plethysmographic peripheral microcirculation in response to a tilt-table test and to 3-month treatment with the highest tolerated beta-blocker (metoprolol) dose in 43 patients aged between 41 and 77 years with acute MI 6 months prior to the start of the study. Before the study the patients were treated with small doses of beta-blocker. Phase differences between HR and peripheral microcirculation oscillations were used to measure the degree of synchronization (*S*), and relative change in *S* from horizontal position was used to characterize the response to vertical tilt.**

Results **Two groups of MI patients matched for clinical characteristics were identified on the basis of the results. 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.**

Conclusion **Assessment of synchronization of 0.1 Hz HR and peripheral microcirculation oscillations as a response to a tilt test can possibly be used as a guideline for selecting beta-blocker dose in post-MI patients.**

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Keywords: 0.1 Hz rhythms, autonomic dysfunction, beta-blockers, coronary heart disease, heart rate variability, metoprolol, microcirculation, synchronization

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Introduction

Beta-blockers play an important role in complex treatment in myocardial infarction (MI) patients with coronary heart disease (CHD).[1–4] 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). In accordance with the contemporary guidelines for beta-blocker treatment, the target dose should be used (e.g. for metoprolol the target dose is 200 mg/day) or, if not tolerated, the highest tolerated dose.[1] However, there is no criterion for controlling beta-blocker treatment based on the functional state of the cardiovascular system (CVS) and interaction between its subsystems. It is known that β_1-type adrenoreceptors are located in the myocardium, whereas β_2-type adrenoreceptors are located in vessels.[5] An open question is the influence of different beta-blockers, for example metoprolol, on the functional interaction between the parts of the CVS.

Heart rate variability (HRV) is a well-known marker of autonomic dysfunction in post-MI patients with CHD.[6–8] Along with classical methods of HRV evaluation, different nonlinear methods have been used in recent years in clinical practice for studying autonomic regulation of the CVS. It is known that operation of the CVS is governed by several rhythmic processes interacting with each other.[9,10] Among them are the rhythms with a basic frequency close to 0.1 Hz observed in HRV,[9–12] arterial pressure[9,10,13] and peripheral microcirculation.[14,15] 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.[14,16–18] Another hypothesis is that they are largely an index of baroreflex gain.[19,20]

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It has been found that 0.1 Hz cardiovascular oscillations can be synchronized between themselves[15,21] to ensure 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.[15,21] 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 based on changes in synchronization between 0.1 Hz oscillations in HR and peripheral microcirculation.

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 43 patients with CHD [19 (44%) females and 24 (56%) males] aged between 41 and 77 years with acute MI 6 months prior to the start of the study.

We used the following criteria to enroll the patients in our study:

1. The confirmed diagnosis of acute MI[2,3,22] about 6 months prior to the start of the study.
2. The absence of systolic dysfunction of the left ventricle (ejection fraction is greater than 50%).
3. Everyday treatment with beta-blockers in doses equivalent to no more than 50 mg/day metoprolol.

For the diagnosis of MI the following criteria were used: detection of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[22]

It should be noted that the choice of patients with the MI remoteness being equal to 6 months is based on the results of our investigation of the degree of synchronization, S, between 0.1 Hz oscillations in HR and peripheral microcirculation within the first year after MI.[23] As has been shown,[23] index S is very low just after MI. It increases during the first 6 months after MI, reaching values on average 1.5 times greater than S values at the first week after MI in the same patient.

Our study included only the patients with no systolic dysfunction of the left ventricle. The exclusion of patients with small values of ejection fraction allowed us to reduce the influence of chronic heart failure on the results of investigation of changes in synchronization index S in response to metoprolol treatment with the highest tolerated dose. The patients with systolic dysfunction of the left ventricle will be enrolled in a further study.

Patients were not included in our study if they matched the following criteria:

1. valvular defect of the heart,
2. abnormalities in HR impeding the analysis of HRV,
3. endocrine pathology except compensated diabetes,
4. symptomatic arterial hypertension,
5. abnormalities in peripheral microcirculation,
6. chronic gastrointestinal diseases (hepatitis, gastric ulcer, duodenum disease and cholecystitis), chronic diseases of kidneys and other chronic diseases in the stage of exacerbation.

The initial group of patients matching the criteria of inclusion in the study consisted of 47 patients. However, four of them were excluded from the study, based on the criteria of exclusion.

To examine autonomic control of the CVS we carried out spectral analysis of HRV and estimated the degree of synchronization between 0.1 Hz rhythms in HR and peripheral microcirculation. ECG, photoplethysmogram (PPG) measured on the middle finger of the patient's hand and respiration were simultaneously recorded during a tilt test before and after 3-month treatment with the highest tolerated metoprolol dose. The tilt test protocol was the following.

1. The patient lay in a horizontal position for a preliminary stage lasting 10 min without signal recording.
2. The signals were recorded within 10 min in the horizontal position of patient's body.
3. The patient was put in a vertical position with a tilt angle of about 80°. To exclude the transients the signals were not registered within 5 min.
4. The signals were recorded within 10 min in the vertical position of patient's body.

The patients were investigated in the afternoon under spontaneous breathing. 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 remained.

The highest tolerated metoprolol dose was selected for each MI patient using titration and taking into account the patient HR and BP. The initial dose of metoprolol was 25 mg/day or 50 mg/day. The dose of metoprolol therapy was increased at 2-week intervals until the target

dose of 200 mg/day was achieved. Titration steps were 50 mg/day (for patients with an initial dose of 25 mg/day), 100 mg/day and 200 mg/day. BP, HR and clinical status were monitored per standard routine during titration.[1] For patients who could not achieve the target dose of metoprolol, the highest tolerated dose was prescribed. The metoprolol dose was selected to be 200 mg/day for 34 (79%) patients and 100 mg/day for 9 (21%) patients.

Data analysis and statistics

Spectral characteristics of HRV were calculated using a parametric method of spectrum estimation based on autoregression model construction. High-frequency range, 0.15–0.4 Hz, and low-frequency range, 0.04–0.15 Hz, of HRV were analyzed.[11]

To estimate synchronization between 0.1 Hz rhythms in HR and peripheral microcirculation we used the method we proposed recently.[15,21] At first we extracted low-frequency 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 $\varphi = \phi_1 - \phi_2$. The presence of 1 : 1 phase synchronization is defined by the condition $|\varphi| < const$.[21] In this case the phase difference $\varphi(t)$ fluctuates around a constant value as shown in Fig. 1(a). After detection of all epochs of synchronization in the plot of $\varphi(t)$ we calculated their total duration S, and expressed it in percentage 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 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.

Fig. 1

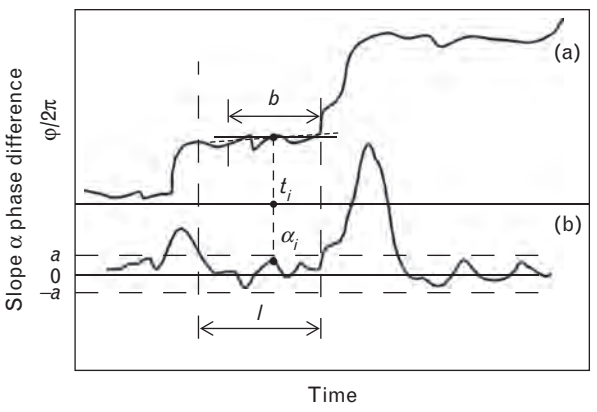


Illustration of the automated procedure for detecting epochs of phase synchronization. (a) Linear approximation of normalized $\varphi(t)$ in a moving window. (b) Slope of the approximating line.

For automated detection of phase synchronization epochs we used the following algorithm 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. 1a). 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. 1b). 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 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 $|\alpha| \leq |a|$, 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. 1b) 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 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.[21] In this study 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 patient several times per day and within several days. The obtained results show that S takes very close values for the data recorded within one day or the next.

We applied the Shapiro–Wilk test to check whether the HRV spectral data are approximately normally distributed. Since these data are non-normal, their further analysis was carried out using nonparametric statistical methods. To compare the variables we used the Mann–Whitney test. 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 was less than 0.05. For a statistical analysis the software package Statistica 6.1 (StatSoft Inc., Tulsa, Oklahoma, USA) was used.

Results

Baseline characteristics of patients are shown in Table 1. Myocardial ischemia in the post-MI patients was assessed from the analysis of ECG, the data of Holter monitor and

Table 1 Baseline characteristics of 43 post-MI patients with CHD

Parameter	All patients ($n=43$)
Age, years, median (25%, 75%)	60 (54, 72)
Female sex, no. (%)	19 (44)
Myocardial ischemia, stenocardia, no. (%)	34 (79)
Angina pectoris events per week, average no. ± variance	24 ± 3
Chronic heart failure with preserved ejection fraction, no. (%)	9 (21)
Hypertension, no. (%)	31 (72)
Prior stroke, no. (%)	4 (9)
Peripheral vascular disease, no.	0
Chronic hepatic failure, no.	0
Diabetes, no. (%)	2 (5)
Chronic obstructive disease of lungs, no.	0
Current or previous smokers, no. (%)	8 (19)
Pathological Q-wave on ECG, no. (%)	27 (63)
Baseline systolic blood pressure, mmHg, median (25%, 75%)	145 (125, 150)
Baseline diastolic blood pressure, mmHg, median (25%, 75%)	85 (80, 90)
Body mass index, median (25%, 75%)	28.3 (23.4, 31.2)
Total cholesterol, mg/dl, median (25%, 75%)	176 (144, 198)
Triglycerides, mg/dl, median (25%, 75%)	86 (78, 110)
Creatinine, mg/dl, median (25%, 75%)	0.81 (0.74, 0.88)
Left ventricular ejection fraction, median (25%, 75%)	59 (54, 65)
Previous treatment	
Antiplatelets, no. (%)	43 (100)
Beta-adrenoceptor blockers, no. (%)	43 (100)
ACE inhibitors, no. (%)	10 (23)
Calcium antagonists, no. (%)	3 (6)
Nitrates, no. (%)	28 (65)
Diuretics, no.	0
Cardiac glycosides, no.	0
Statins, no. (%)	40 (93)

ACE, angiotensin-converting enzyme; CHD, coronary heart disease; MI, myocardial infarction.

complaints of patients. As can be seen from Table 1, 9 (21%) patients had chronic heart failure with preserved ejection fraction. The diagnosis of chronic heart failure with preserved ejection fraction was confirmed using echocardiography if the following three conditions were satisfied: presence of signs and/or symptoms of chronic heart failure, presence of normal left-ventricular systolic function (ejection fraction is greater than 50%), evidence of diastolic dysfunction (abnormal left-ventricular relaxation or diastolic stiffness).[24]

Before inclusion into this study all patients were treated in accordance with contemporary recommendations for acute coronary syndrome treatment and stable angina pectoris treatment within 6 months after acute MI.[2,3,25] The list of drugs given to patients before the study is presented in Table 1. Reperfusion or revascularization procedures were not carried out for these patients.

After 3-month treatment with the highest tolerated metoprolol dose the average 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 changes in values of BP were not statistically significant in all patients during our study (Table 2). This observation may be explained probably by the fact that all the patients were treated with small doses of metoprolol before the beginning of our study.

We studied relative changes in degree S of synchronization between 0.1 Hz rhythms in HR and peripheral microcirculation as a response to vertical tilt before and after 3-month treatment with the highest 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 matched for clinical characteristics 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). 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. 2). This group was named as Tilt ($S+$) patients.

After 3-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. 2).

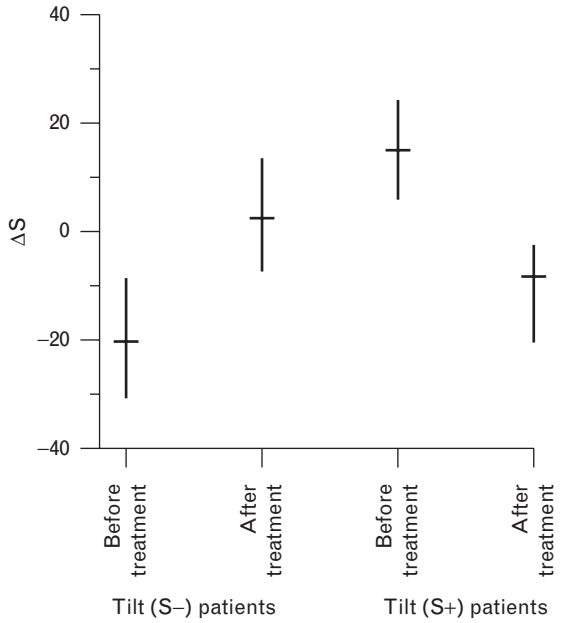
To illustrate individual changes in ΔS we plotted the individual ΔS values for patients from the groups of Tilt

Table 2 Estimated BP, *S* and HRV parameters in Tilt (*S*−) and Tilt (*S*+) MI patients before and after three-month metoprolol treatment with the highest tolerated dose

Parameter	Body's position	Tilt ($S-$) patients ($n=20$)		Tilt ($S+$) patients ($n=17$)	
		Before treatment	After treatment	Before treatment	After treatment
BP_{mean}, mmHg	Horizontal	120 (110, 133)	113 (106, 136)	123 (110, 128)	116 (108, 133)
S, %	Horizontal	41 (29, 48)	27 (22, 41)*	26 (19, 29)+	37 (27, 43)*,+
	Vertical	19 (11, 25)	32 (25, 37)*	37 (33, 43)+	24 (19, 33)*,+
HR, s^{-1}	Horizontal	73 (60, 81)	66 (55, 74)*	71 (66, 78)	68 (59, 73)*
	Vertical	80 (69, 88)	72 (59, 80)*	83 (75, 89)	75 (64, 81)*
LF, ms^2	Horizontal	87 (48, 147)	114 (58, 192)	145 (60, 260)+	208 (74, 435)*,+
	Vertical	99 (36, 321)	66 (41, 122)	138 (54, 167)	96 (59, 262)+
HF, ms^2	Horizontal	151 (65, 257)	170 (90, 218)	107 (55, 299)	178 (68, 378)
	Vertical	92 (34, 163)	76 (34, 160)	47 (26, 110)+	102 (24, 232)+

The data are shown as Me (25%, 75%). *Significant difference ($P < 0.05$) from parameter values before metoprolol treatment. +Significant difference ($P < 0.05$) from the same parameter in Tilt (S−) patients. $BP_{mean} = DBP + \frac{SBP-DBP}{3}$, where BP_{mean} is the mean arterial pressure, DBP is the diastolic blood pressure and SBP is the systolic blood pressure. HF, high frequency; HR, heart rate; HRV, heart rate variability; LF, low frequency; MI, myocardial infarction.

Fig. 2



Change in S as a response to vertical tilt in Tilt ($S-$) and Tilt ($S+$) MI patients before and after 3-month metoprolol treatment with the highest tolerated dose. Medians with inter-quartile ranges (25%, 75%) are shown.

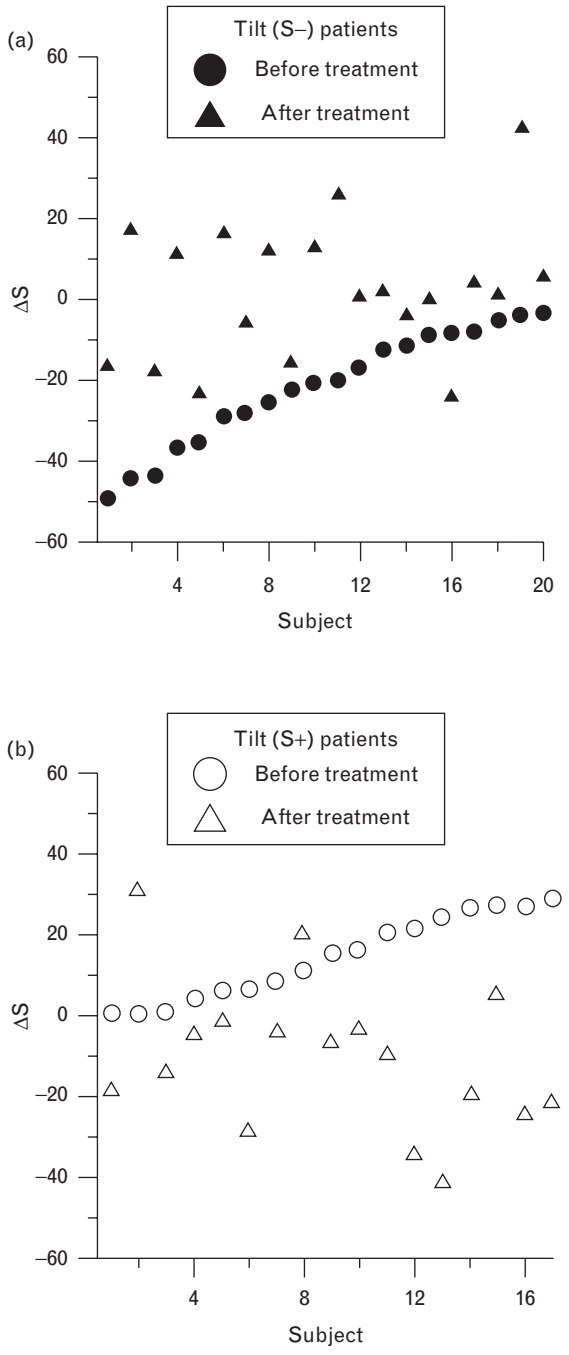
($S-$) and Tilt ($S+$) MI patients at the beginning of the study and after 3-month treatment with the highest tolerated metoprolol dose (Fig. 3).

Note that before metoprolol treatment S values in MI patients in the vertical position were significantly greater in Tilt ($S+$) patients than in Tilt ($S-$) patients ($P=0.006$) (Table 2). After 3-month metoprolol treatment with the highest tolerated dose, S values in the vertical position became significantly greater in Tilt ($S-$) patients than in Tilt ($S+$) patients ($P=0.02$) (Table 2).

After metoprolol treatment a decrease of HR was observed in both groups of patients (Table 2). The power of low-frequency 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 high-frequency band in HRV spectrum was lower in Tilt ($S+$) patients than in Tilt ($S-$) patients ($P=0.04$). After 3-month metoprolol treatment the high-frequency band power became greater in Tilt ($S+$) patients than in Tilt ($S-$) patients ($P=0.05$) (Table 2).

We have not revealed dependence of S on the power of HRV spectrum in low-frequency and high-frequency bands 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.

Fig. 3



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

Discussion

We have shown that after 3-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. Probably,

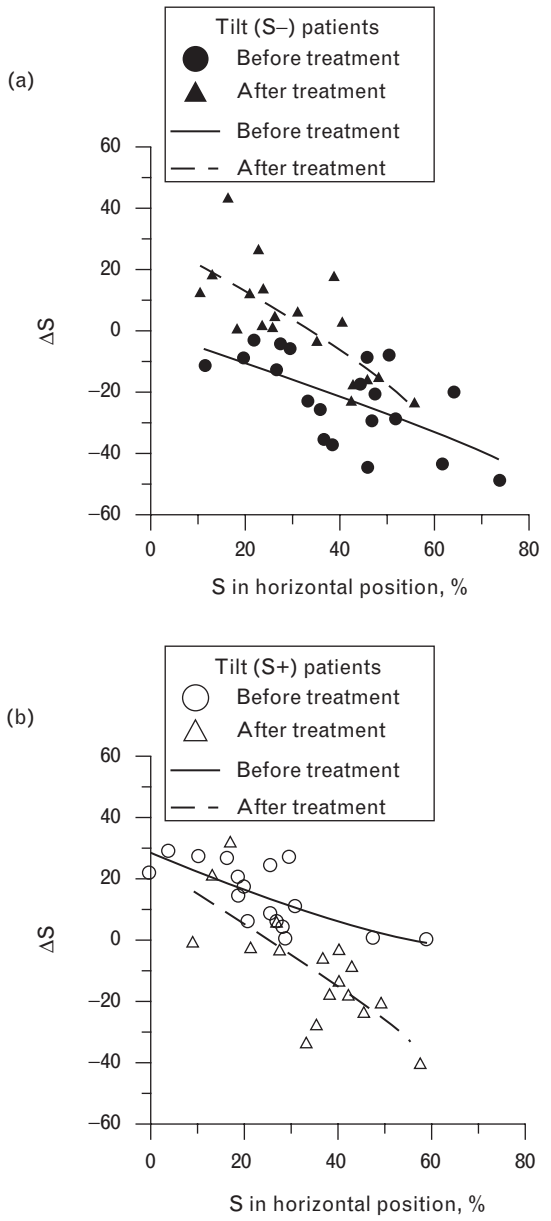
the revealed distinctions between the groups of MI patients are caused by cardioselectivity of metoprolol influence on β_1-type adrenoreceptors. Blocking of β_1-type adrenoreceptors modulates the activity of heart autonomic regulation mechanisms at 0.1 Hz due to the changes of feedback loop features.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

After 3-month treatment with the highest tolerated metoprolol dose the Tilt ($S-$) MI patients had significantly lower power of low-frequency band in HRV spectrum than Tilt ($S+$) patients. This means that the activity of autonomic regulation of the 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 peripheral microcirculation regulation can be restored, leading to an increase of S values. Note that healthy individuals have high values of S.[15] In Tilt ($S+$) patients the low-frequency 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 a decrease of S.

In Fig. 4 we plot the dependence of ΔS on the value of S in the horizontal position for each group of MI patients before and after treatment with the highest tolerated metoprolol dose. As can be seen from Fig. 4, after metoprolol treatment the approximation curve shifts up in Tilt ($S-$) MI patients and below in Tilt ($S+$) MI patients. The 3-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.

For the combined group of Tilt ($S-$) and Tilt ($S+$) post-MI patients with CHD there is no any shift of approximation curve after metoprolol treatment (Fig. 5). We assume the existence of optimal S values in MI patients under beta-blocker treatment. It should be noted that based on the results of our study six MI patients were not attributed to Tilt ($S-$) or Tilt ($S+$) patients because after 3-month metoprolol treatment they had change in ΔS less than 5%. We assume that these patients had already optimal S values before treatment. The increase of beta-blocker dose in these patients did not cause significant change in ΔS, that is, S values remained in the optimal range. This fact counts in favor of our assumption of the presence of a range of optimal values of S in MI patients. Since MI patients in our study are divided into groups of Tilt ($S-$) and Tilt ($S+$) patients depending only on the sign of ΔS before the treatment, the patients with optimal S values cannot be revealed at the beginning of the study. They will be treated as well as other patients from the same group. However, the choice of optimal dose of beta-blocker treatment can be corrected based on the results of a tilt test repeated in 3 months and taking into account other clinical criteria.

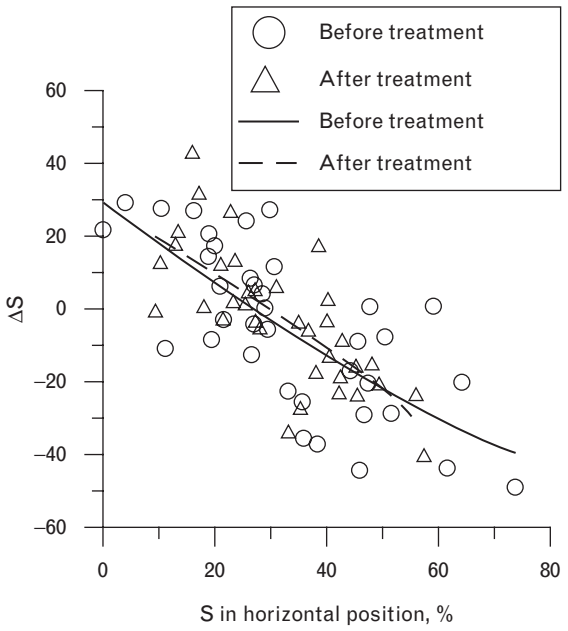
Fig. 4



Approximation curves for dependence of ΔS on S in the horizontal position before and after 3-month metoprolol treatment with the highest tolerated dose in Tilt ($S-$) and Tilt ($S+$) MI patients.

At present time there is no doubt that MI patients with CHD should be treated with beta-blockers.[25] It has been shown that beta-blockers improve autonomic function in such patients and decrease fatal risk.[26–39] It is believed that beta-blocker dose for post-MI patients should be the highest tolerated one.[1] On the contrary, the increase of

Fig. 5



Approximation curves for dependence of ΔS on S in the horizontal position before and after 3-month metoprolol treatment with the highest tolerated dose for the combined group of Tilt ($S-$) and Tilt ($S+$) MI patients.

beta-blocker dose up to the highest tolerated one is not always justified. In addition, gender-specific differences in the pharmacokinetics of beta-blockers lead to greater drug exposure in women.[40–52]

In our study we revealed the different influence of beta-blocker treatment on the synchronization of 0.1 Hz HR and peripheral microcirculation oscillations in MI patients. The response to a tilt test in Tilt ($S-$) patients is 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 is 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 the CVS.

The results of our study show that assessment of synchronization index S 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 cost 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, the decrease in S is the major factor of fatal risk in post-MI patients.[23]

It should be noted that one could try to get clinically useful information for treatment of MI patients using other measures, which characterize the activity in low-frequency band. For example, prevalent low-frequency oscillation (PLF) of heart rate is shown to be a potent risk predictor in post-MI patients.[53]

Study limitations

Our study included only 43 post-MI patients. It is rather a small sample, but our study was a prospecting one, which can give rise to more representative investigations of synchronization index S potential for selecting an optimal beta-blocker dose. Apart from this, we used a number of criteria to enroll the patients in the study and to exclude them from the study (see the Methods section). However, the number of patients excluded for various reasons from the study was only four (9%).

The increase of beta-blocker dose in six (14%) MI patients did not cause a significant change in ΔS. For such patients the choice of the optimal dose of beta-blocker treatment should be corrected based on the results of a tilt test repeated in 3 months. Another limitations is that we did not evaluate the effects of beta-blocker with coronary vasodilatators.[54,55]

To conclude, in our study we revealed that autonomic regulation of CVS in post-MI patients with CHD is characterized by individual sensitivity to the increase of beta-blocker dose from the small dose to the highest tolerated one. In particular, two groups of MI patients were identified, which showed opposite changes in S in response to a tilt test after 3-month metoprolol treatment. Before beginning of the study the patients from one of these groups showed decreased S as a response to vertical tilt, whereas the patients from another group showed increased S.

We assume that assessment of synchronization of 0.1 Hz HR and peripheral microcirculation oscillations as a response to a tilt test can possibly be useful for selecting an optimal dose of beta-blocker treatment in post-MI patients. Prescription of high doses of beta-blocker to patients with increased S as a response to vertical tilt 6 months after acute MI (about 40% of all post-MI patients) should probably be avoided or done with care, since it increases autonomic dysfunction of CVS.

The results of our study indicate the necessity of further investigations for the development of criteria for selection of the optimal dose of beta-blocker treatment in MI patients.

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