Synchronization of low-frequency oscillations in the human cardiovascular system

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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 method is proposed for quantitative estimation of synchronization between these oscillating processes based on calculation of relative time of phase synchronization of oscillations. It is shown that healthy subjects exhibit on average substantially longer epochs of internal synchronization between the low-frequency oscillations in heart rate and blood pressure than patients after acute myocardial infarction. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3187794]

The human cardiovascular system (CVS) 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 and blood pressure with a basic frequency close to 0.1 Hz having a great importance for maintaining cardiovascular homeostasis. The origin of these LF oscillations is still a subject of controversy. According to one hypothesis, the 0.1 Hz oscillations in heart rate and blood pressure are largely an index of baroreflex gain. On another hypothesis, these oscillations have a central origin and represent an intrinsic property of autonomous neural network. We have investigated interaction between the 0.1 Hz cardiovascular oscillations in healthy subjects and patients after acute myocardial infarction (AMI). Peculiarities of interaction of the elements of CVS reflect its state and may contain useful information for medical diagnostics. The interaction between the rhythms is studied using a phase synchronization measure based on the Hilbert transform. A method is proposed for quantitative estimation of synchronization by using an algorithm of automated detection of phase synchronization epochs. The method is based on a linear approximation of instantaneous phase difference of analyzed signals in a moving window. Recommendations on a choice of the method parameters ensuring its high efficiency are given. A statistical significance of the calculated synchronization measure is analyzed using surrogate data. It is shown that healthy subjects exhibit on average substantially longer epochs of synchronization between the LF oscillations in heart rate and blood pressure than patients after AMI. Arguments are adduced in favor of the concept that oscillations of heart rate and blood pressure with a frequency of about 0.1 Hz have a central origin. Moreover, these oscillations may be considered as different processes that exhibit a comparatively high internal synchronization between themselves in healthy subjects ensuring a high adaptability of the CVS.

I. INTRODUCTION

Investigation of interactions between various oscillating processes governing the dynamics of a human CVS attracts a lot of attention.[1] The interest to this problem is motivated by the fact that peculiarities of functioning and interaction of the elements of CVS reflect its state and may contain useful information for medical diagnostics. The longest history has the investigation of interdependence between the heart beat and respiration. Due to their interaction the heart rate increases during inspiration and decreases during expiration. This respiratory modulation of the heart rate is known as respiratory sinus arrhythmia.[2] It has been found that the main heart rhythm and respiration can be synchronized.[3–10] Moreover, the epochs of cardiorespiratory synchronization has been found to be longer in athletes[3] than in subjects performing recreative activity.[4,6]

Besides the oscillations at a frequency of respiration named high-frequency (HF) ones and observed usually in the range 0.15–0.4 Hz, the human heart rate exhibits LF oscillations with a basic frequency of about 0.1 Hz.[11,12] The HF and LF oscillations are observed also in the signals of blood pressure[11,12] and blood flow.[13,14] These oscillations are of great importance for maintaining cardiovascular homeostasis. Unlike respiratory frequency oscillations, the LF cardiovascular oscillations appear spontaneously across a frequency range from 0.04 to 0.15 Hz, although generally close to 0.10 Hz. The origin of these oscillations is still a subject of controversy.[15,16] A number of research groups supports the central oscillator theory believing that 0.1 Hz oscillations of heart rate and blood pressure represent an intrinsic property of autonomous neural network.[17–19] On another hypothesis,

these LF oscillations are largely an index of baroreflex gain.[20,21]

It has been found that 0.1 Hz cardiovascular oscillations can be synchronized with the main heart rhythm[22] and respiration.[7,23] Interdependence between the LF oscillations in blood pressure and heart rate has also been studied.[24,25] One of the most widespread tools used to investigate this interdependence is based on the analysis of power spectra and coherence between the signals. Such approach allows one to estimate in the frequency domain the strength of linear coupling between the signals. However, the cardiovascular rhythms are known to be nonlinearly mutually interacting as a result of the presence of both feedback and feedforward coupling mechanisms.[26] Moreover, the signals under consideration are usually nonstationary. Their frequencies and amplitudes can be highly variable within the time of observation. In such a situation nonlinear measures of synchronization[27,28] may be preferred over the coherence function.

In this paper the interaction between the oscillating processes with a frequency of about 0.1 Hz in heart rate and blood pressure is studied using a quantitative measure based on the analysis of phase synchronization of oscillations. We compare a degree of synchronization between the abovementioned LF oscillations in healthy subjects and patients after AMI. The obtained results are discussed in detail.

II. EXPERIMENTAL DATA AND METHODS OF THEIR ANALYSIS

A. Description of measurements and data preprocessing

We studied 17 healthy subjects (8 women) aged 20–48 years and 42 patients (14 women) aged 41–80 years after AMI. The study was approved by the institutional ethical board and all subjects gave their written informed consent. The signals of electrocardiogram (ECG) and blood pressure on the middle finger of the subject's hand were simultaneously recorded in a supine resting condition under spontaneous breathing. All signals were sampled at 250 Hz and digitized at 16 bits for off-line analysis with a personal computer. The duration of each record was 10 min. 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.

Figures 1(a) and 1(b) show short segments of a typical experimental record. Extracting from the ECG signal a sequence of *R-R* intervals, i.e., a series of time intervals between the two successive *R* peaks, we obtain information about the heart rate variability (HRV). To obtain equidistant time series from not equidistant sequence of *R-R* intervals we approximate it with cubic splines and resample with a frequency of 5 Hz [Fig. 1(c)].

Spectral analysis of *R-R* intervals reveals different frequency domains of HRV. Generally the Fourier power spectrum of *R-R* intervals exhibits well-distinguished characteristic peaks at frequencies f_r and f_v associated with the respiratory and LF fluctuations of heart rate, respectively [Fig. 2(a)]. Besides the HF range, 0.15–0.4 Hz, and LF range, 0.04–0.15 Hz, containing the peaks f_r and f_v, respectively, a very LF range, <0.04 Hz, is defined in the HRV power spectrum.[29] A power spectrum of blood pressure signal also exhibits peaks at frequencies f_r and f_v associated with the respiratory and LF oscillations of blood pressure, respectively [Fig. 2(b)]. In this paper we consider only oscillations relating to the LF range of power spectra.

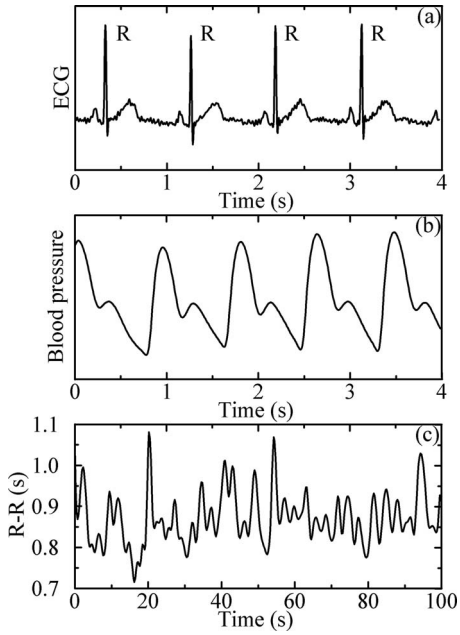

FIG. 1. Segments of (a) an ECG signal, (b) a blood pressure signal, and (c) a sequence of *R-R* intervals. ECG and blood pressure signals are given in arbitrary units.

To extract the LF (slow) component of HRV associated with a process of heart rate regulation with a frequency of about 0.1 Hz let us filter the sequence of *R-R* intervals removing the HF oscillations (>0.15 Hz) associated predominantly with respiration and very LF oscillations (<0.05 Hz). Similarly, we extract the LF component of blood pressure signal by using the same filtration with the bandpass of 0.05–0.15 Hz.

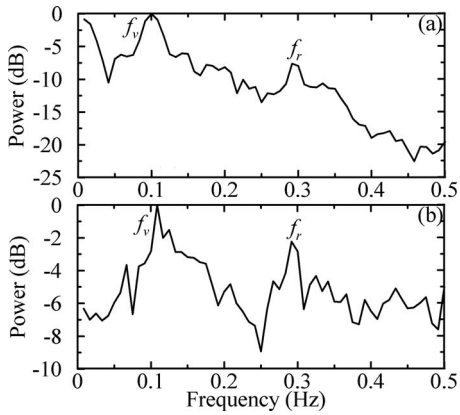

FIG. 2. Typical Fourier power spectra of (a) *R-R* intervals and (b) blood pressure signal. The frequencies f_r and f_v are associated with the respiratory and LF oscillations, respectively, in both signals.

B. Method of detection of phase synchronization between the 0.1 Hz rhythms

To investigate the interaction between the oscillating processes in blood pressure and heart rate whose fundamental frequencies are close to 0.1 Hz we use a phase synchronization measure based on the Hilbert transform. Since we deal with a passive experiment in which it is not possible to vary the system parameters and coupling, the analysis of synchronization is based on the assumption that the observed signals are generated by two interacting self-sustained oscillators.[30] The validity of this assumption is discussed in detail in Sec. IV.

The first step in quantifying phase synchronization between two signals is to determine their phases. To calculate the phase of LF oscillations of heart rate we construct the analytic signal $\zeta(t)$ (Refs. 31 and 32) 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

$$\zeta(t) = s(t) + i\tilde{s}(t) = A(t)e^{i\phi(t)}, \tag{1}$$

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 $s(t)$,

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

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

$$\phi(t) = \arctan\frac{\tilde{s}(t)}{s(t)}. \tag{3}$$

In a similar way the phase of LF oscillations of blood pressure is calculated from the filtered signal of blood pressure.

To detect synchronization between the LF blood pressure and heart rate oscillations we calculate the phase difference

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

where ϕ_p is the phase of LF oscillations of blood pressure and ϕ_h is the phase of LF oscillations of heart rate. The presence of 1:1 phase synchronization is defined by the condition $|\varphi| < \text{const}$.[33] In this case the phase difference $\varphi(t)$ fluctuates around a constant value. Strictly speaking, a passive experiment can reveal only the presence of interaction rather than synchronization.[30] However, the methods of analysis of phase relationships are based on the concept of synchronization. Thus, following a common practice,[3,4,27,33] we use the corresponding terminology.

We detect all epochs of synchronization in the plot of $\varphi(t)$, calculate their total duration, and express it in percentage of the duration T of the entire record. Let us name the obtained measure as the total percentage of phase synchronization,

$$S = \frac{\Sigma_{k=1}^{N} d_k}{T} \times 100\%, \tag{5}$$

where d_k is the duration of the kth epochs of synchronization and N is the number of epochs.

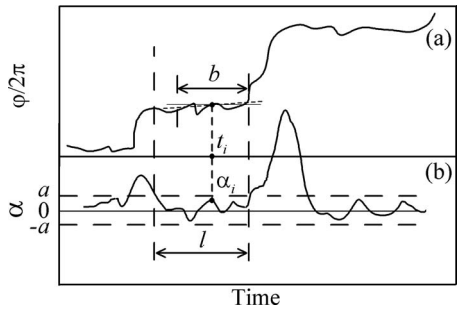

FIG. 3. Illustration of the automated procedure for detecting epochs of phase synchronization. (a) Linear approximation of normalized $\varphi(t)$ in a moving window. (b) Slope of the approximating line.

For automated detection of phase synchronization epochs we developed an 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. 3(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. 3(b)]. Moving the window by one point along the time series of $\varphi(t)$, 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 $\varphi(t)$ 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. 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. 3(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 $\varphi(t)$ whose duration is equal to $b/2$. A similar method of automated detection of cardiorespiratory synchronization was used by Bartsch *et al.*[9] 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 total percentage of phase synchronization decreases with decreasing in $|a|$ or increasing in l. The dependence of S on the parameter b is not monotonous. Choosing 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 and ensure a statistical significance of the results (see Sec. II C). We found that these conditions are satisfied if l is about one to two characteristic periods of oscillations, b is close to the characteristic period, and $|a|$ is about 0.005–0.01. Further we use the following fixed values of the parameters for the investigation of all experimental records: $b=13$ s, $|a|=0.01$, and $l=16$ s.

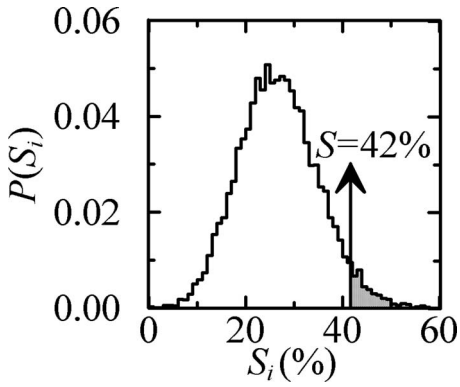

FIG. 4. Distribution of the total percentage of phase synchronization S_i constructed from the ensemble of surrogate data. The vertical line indicates $S=42\%$ calculated from experimental data.

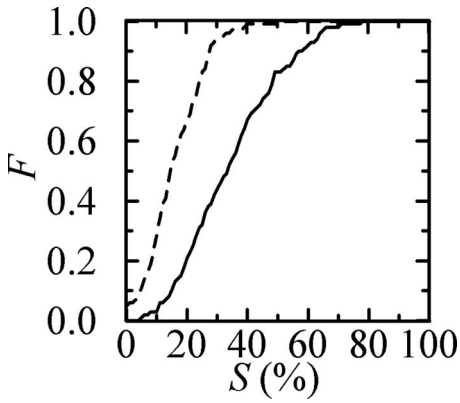

FIG. 5. Distribution functions of the total percentage of phase synchronization between the cardiovascular rhythms with a frequency of about 0.1 Hz in healthy subjects (solid line) and AMI patients (dashed line) calculated over all records.

C. Estimation of statistical significance of results

Analyzing experimental data for which nonstationarity, noise presence, short length of time series, or closeness of basic frequencies is typical, one can detect spurious synchronization even between noncoupled oscillators and come to wrong conclusions. Therefore, it is important to estimate a statistical significance of the synchronization analysis results. We estimate a statistical significance of synchronization measure S calculation by using surrogate data[34] often applied to investigation of experimental time series.

To analyze a significance of the obtained results we exploit the following procedure. At first, from each signal of blood pressure and *R-R* intervals filtered with the bandpass of 0.05–0.15 Hz we generate surrogate time series by multiplying the Fourier transform of the original data by random phases and then transforming back to the time domain. This method of surrogate data preparation preserves periodograms of the analyzed signals but destroys couplings between them. Then, with the help of the automated procedure of phase synchronization detection we calculate a total percentage of phase synchronization S_i, $i=1,\ldots,M$, where $M=10\,000$, for each ith pair of surrogates. Over the whole ensemble of surrogates we plot a distribution P of S_i values. Figure 4 shows a distribution $P(S_i)$ constructed using surrogate data prepared from the filtered signals of blood pressure and *R-R* intervals of one of the subjects. The vertical line indicates the value of S calculated from original signals. A level p of statistical significance for the value of S calculated from experimental data can be estimated as the ratio of area of distribution $P(S_i)$ corresponding to $S_i \geq S$ (shown as shaded region in Fig. 4) to the entire area of distribution. For the case depicted in Fig. 4 $p=0.03$. It means that probability of accidental obtaining of $S=42\%$ from experimental data is not greater than 0.03.

III. RESULTS

Using the proposed method we calculated the total percentage of phase synchronization between the 0.1 Hz rhythms for all subjects. Figure 5 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 on average in healthy subjects than in AMI patients. In our experiments S took the values $34.4\% \pm 16.1\%$ (mean $\pm$ 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 Sec. II B. However, in a wide range of these parameters variation the value of S remains on average considerably greater in healthy subjects than in AMI patients.

Using the method based on surrogate data (see Sec. II C) we estimated a statistical significance of every value of S calculated from experimental data. The obtained results are presented in Fig. 6. The total percentage of phase synchronization and its level of significance are shown by circles for healthy subjects and by crosses for AMI patients. The horizontal line indicates a significance level of $p=0.05$ which is often used in practice to provide sufficiently high reliability. The results of our study show that about one-half of records of both healthy subjects and AMI patients exhibit S values corresponding to a 0.05 significance level conclusion that coupling between the processes is present, i.e., the conclusion of coupling presence has a confidence probability of 0.95. As can be seen from Fig. 6, a separation of circles and crosses is better in the lower part of the figure corresponding to significant S.

The distribution functions of the total percentage of phase synchronization calculated only for S values significant at a 0.05 level are presented in Fig. 7(a) for both groups of subjects. S took the values $46.4\% \pm 12.7\%$ for healthy subjects and $21.9\% \pm 8.1\%$ for AMI patients. Figure 7(a) is

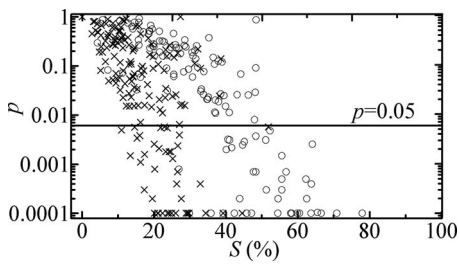

FIG. 6. Level of statistical significance of the total percentage of phase synchronization for healthy subjects (circles) and AMI patients (crosses).

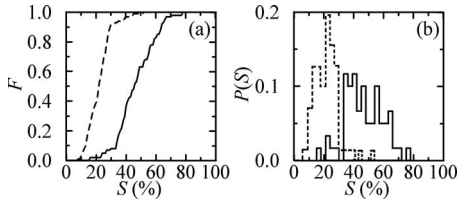

FIG. 7. (a) Distribution functions of significant S values for healthy subjects (solid line) and AMI patients (dashed line). (b) Distributions of significant S values for healthy subjects (solid line) and AMI patients (dashed line).

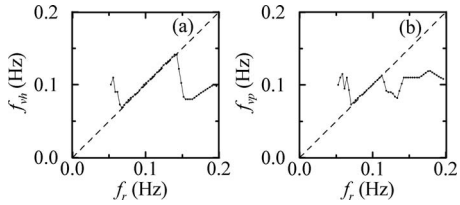

FIG. 8. (a) Dependence of the frequency of heart rate LF oscillations on the frequency of respiration for one of the healthy subjects. (b) Dependence of the frequency of blood pressure LF oscillations on the frequency of respiration for the same subject.

qualitatively similar to Fig. 5 but exhibits appreciably smaller region of overlapping of distribution functions. Hence, the choice of only significant S values allows one to improve separation of the considered groups of subjects.

Figure 7(b) gives another presentation of S values corresponding to a 0.05 significance level conclusion that processes are coupled. In this figure the distributions $P(S)$ are plotted separately for healthy individuals and AMI patients. In healthy subjects S took the values from 15% to 78% and in AMI patients from 7% to 52%. These distributions are noticeably different and have a small area of overlapping.

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 six months after AMI. Only several subjects took part in this investigation and only four of them showed the values of the total percentage of phase synchronization significant at a 0.05 level both during the first three weeks after AMI and after six months after AMI. Three of these subjects showed a pronounced increase in S 1.5 times on average in comparison with their own S values during the first three weeks after AMI. One subject showed a small decrease in S 1.1 times. However, these S values after six months after AMI were less on average in comparison with average S values in healthy subjects.

IV. DISCUSSION

The analysis of synchronization carried out in our paper is based on the assumption that 0.1 Hz oscillations of blood pressure and heart rate are generated in different central neural structures involved in the autonomic regulation of the CVS. Several facts count in favor of this hypothesis. First, the concept of a central origin of the LF cardiovascular oscillations is supported by animal studies. In vagotomized and sinoaortic denervated cats an activity of medullary neurons involved in the regulation of cardiovascular function contains distinct LF oscillatory component, which is correlated with blood pressure variability.[18] Second, the results of experiments where the LF oscillations were present only in one of the signals, either blood pressure or R-R intervals, 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 HRV in supine humans by using a fixed-rate cardiac pacing with electrical stimuli did not alter LF arterial pressure oscillations.[35] On the other hand, implantation of a left ventricular assist device in patients with severe heart failure restores the LF oscillations in R-R intervals of the native heart, even in the absence of any LF oscillations in blood pressure.[19] After such implantation the native heart remains innervated and continues to be regulated by the autonomic nervous system while interactions between R-R intervals and blood pressure are absent.[19]

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 the different response of the LF heart rate and blood pressure oscillations to external stimulation. Oscillatory lower body negative pressure at 0.1 Hz increases both LF blood pressure and R-R interval oscillations.[24] However, cross-spectral coherence between these increased oscillations becomes highly variable both among subjects and across stimulus level.[24] Furthermore, the frequencies of the LF cardiovascular rhythms can be locked by a signal of stimulation in the form of neck suction with the frequency continuously increasing from 0.02 up to 0.20 Hz.[13] Note that R-R intervals exhibit a wider range of frequency locking by external stimulation than blood pressure.[13]

We observed a similar effect studying in healthy subjects the external synchronization of the LF cardiovascular rhythms by respiration with the frequency continuously increasing from 0.05 to 0.20 Hz within 18 min. Figure 8(a) shows a typical dependence of the frequency of heart rate slow oscillations f_{vh} on the frequency of respiration f_r. In Fig. 8(b) a dependence of the frequency of blood pressure slow oscillations f_{vp} on the respiratory frequency is displayed. The frequencies f_r, f_{vp}, and f_{vh} are defined as the frequencies at which the main peaks are observed in the power spectra of the signal of respiration and the filtered signals of blood pressure and R-R intervals, respectively. The power spectra of these three signals are computed in a moving window. The presence of 1:1 frequency locking is clearly seen within the interval 0.068–0.142 Hz in Fig. 8(a) and within the interval 0.071–0.113 Hz in Fig. 8(b). Thus, the experiment with the frequencies of respiration close to the basic frequency of the LF heart rate and blood pressure oscillations exhibits a frequency locking phenomenon typical for a classical self-sustained oscillator under external forcing. Different widths of synchronization band for the considered rhythmic processes are consistent with the hypothesis that different self-sustained oscillators generate these rhythms. Mutual interactions between the LF oscillations of heart rate and LF oscillations of blood pressure result in these rhythms synchronization, which can be regarded as the internally induced one.

A comparison of different synchronization measures did not reveal in general case a considerable advantage of any measure over the other ones.[27,28,36] The measure should be chosen according to the quality and type of data.[28] Since the LF oscillating processes in CVS exhibit complex nonlinear interactions and the frequencies and amplitudes of these processes can be variable within the experiment, the considered phase synchronization measure based on the analysis of instantaneous phase difference seems to be more suitable for investigation of synchronization than usually used coherence function. For the signals under examination a situation is typical where their frequencies are varied while the frequency ratio remains stable. In this case the sensitivity of phase synchronization analysis may be higher than that of coherence. In our study the values of the total percentage of phase synchronization were significant more often than the values of coherence function.

The high values of synchronization measure for 0.1 Hz oscillations in blood pressure and heart rate that have been found in our study for healthy subjects indicate qualitative functional interaction between the mechanisms of blood pressure and heart rate regulation, which ensures a high adaptability of the CVS. However, this interaction may be disturbed in various cardiovascular pathologies, e.g., AMI. Breakdown (partial or total) of functional couplings between the systems of slow regulation of heart rate and blood pressure leads to desynchronization of 0.1 Hz oscillations.

The evidence that substantial decrease in the total percentage of phase synchronization 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. First, at a spontaneous breathing the variability of the phase shift between blood pressure and heart rate fluctuation near the frequency of 0.1 Hz is similar in young versus older healthy subjects.[25] Second, as we have observed, the subjects after six months after AMI show on average a pronounced increase in S in comparison with themselves during the first three weeks after AMI. This observation suggests that the functional couplings in the autonomic control system of the CVS may be gradually restored after AMI.

V. CONCLUSION

We have investigated interaction between the oscillating processes with a frequency of about 0.1 Hz observed in the human heart rate and blood pressure. The method is proposed for quantitative estimation of synchronization between these processes based on calculation of the total percentage of phase synchronization of oscillations. The method of automated detection of phase synchronization epochs is developed. This method is based on a linear approximation of instantaneous phase difference of analyzed signals in a moving window. Recommendations on a choice of the method parameters ensuring its efficiency are given. A statistical significance of the calculated synchronization measure is analyzed using surrogate data.

We have detected for the first time the presence of synchronization between the 0.1 Hz oscillations in heart rate and blood pressure. It has been found that healthy subjects show on average substantially longer epochs of synchronization between the LF cardiovascular rhythms than patients after AMI. The obtained results support the concept that 0.1 Hz oscillations in heart rate and blood pressure have a central origin. Moreover, our results count in favor of the conclusion that these oscillations are generated in different central neural structures involved in the autonomic control of the CVS. Optimal adjustment between the LF cardiovascular rhythms resulting in their comparatively high internal synchronization ensures a high adaptability of the CVS that is necessary for global healthy behavior of the organism. However, this synchronization may be deteriorated at AMI leading to a disruption of natural functional couplings within the system of the CVS autonomic regulation. Thus, the analysis of synchronization between the LF oscillations in heart rate and blood pressure seems to be promising for studying a degree of disruption of autonomic regulation of the CVS and for controlling the efficiency of medical treatment and rehabilitation.

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