# Synchronization between main rhythmic processes in the human cardiovascular system

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For the cases of spontaneous respiration and paced respiration with a fixed frequency and linearly increasing frequency, we investigate synchronization between three main rhythmic processes governing the cardiovascular dynamics in humans, namely, the main heart rhythm, respiration, and the process whose fundamental frequency is close to 0.1 Hz. The analysis of the experimental records reveals synchronous regimes of different orders $n:m$ between all the three main rhythms. The influence of the regime of breathing and the magnitude of heart rate variability on the degree of synchronization is considered.

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## I. INTRODUCTION

Complex rhythmic processes interacting with each other are typical in living organisms [1,2]. A striking example of such interaction between various physiological rhythms is the operation of the human cardiovascular system (CVS). The main heart rhythm with a frequency of about 1 Hz generated by the cardiac pacemaker, respiration whose frequency is usually around 0.25 Hz, and the process of blood pressure and heart rate regulation affected by the sympathetic nerve activity and baroreflex loop and having in humans the fundamental frequency close to 0.1 Hz [3] are the most significant oscillating processes governing the cardiovascular dynamics.

The earliest inter-relation between these rhythms to be identified, and the most frequently investigated, is that between the respiratory and cardiac rhythms. 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 (RSA) [4,5]. The question of whether RSA originates mainly from a central coupling between respiration and heart rate [6,7] or from baroreflex mechanism [8] is still a subject of controversy. Recently, it has been found that the main heart rhythm and respiration can be synchronized [9–15]. Besides, it has been shown that cardiorespiratory synchronization tends to become weaker with increasing respiratory modulation of the heart rate, and concluded that these effects are two competing aspects of cardiorespiratory interaction [9,12,13].

The third significant rhythmic process operating within the CVS, namely, the process with a frequency $f_v \approx 0.1$ Hz associated with the self-sustained blood pressure oscillations (Mayer wave) and low-frequency oscillations in the heart rate [Mayer wave sinus arrhythmia (MWSA)] has been intensively studied [3,16–21]. However, the ability of these rhythms to become synchronized to the respiratory and cardiac rhythms with frequencies $f_r$ and $f_h$, respectively, invites further investigation.

Investigation of heart rate variability (HRV) data from healthy human subjects performed in Ref. [14] has shown that the interaction of the three main rhythms within the cardiovascular system can be considered as weak and the rhythm with frequency $f_v$ is nonsynchronous with either of the two other rhythms. Phase synchronization in the statistical sense [12] between the spontaneous respiration and the process whose period is about 10 s has been reported in Ref. [22]. Interaction between the main heart rhythm and the process with frequency $f_v$ has been studied mainly in terms of physiology [3,6,21] and in the models [18,23,24]. Note that the model proposed in Ref. [23] has demonstrated entrainment between these two rhythms.

In this paper we systematically study synchronization between the rhythm with the basic frequency of about 0.1 Hz and the two other rhythms (respiration and heartbeat) under different regimes of breathing. The influence of the magnitude of respiratory and low-frequency fluctuations of the heart rate, i.e., RSA and MWSA, on the degree of synchronization between main rhythms is investigated.

The paper is organized as follows. In Sec. II we describe the experiments performed and the techniques used for data processing. Section III presents results of investigation of synchronization between the three main rhythms within the human cardiovascular system for the cases of spontaneous respiration, fixed-frequency respiration, and respiration with linearly increasing frequency. Section IV contains a discussion. In Sec. V we summarize our results.

## II. DESCRIPTION OF MEASUREMENTS AND METHODS OF DATA PROCESSING

We studied seven healthy volunteers. They were men aged 20–34 years, having average levels of physical activity. The electrocardiogram (ECG) and respiratory signals were simultaneously measured in the sitting position. All signals were recorded with the sampling frequency 250 Hz and 16-bit resolution.

Four experiments were performed with each subject under different regimes of breathing. First, the signals were registered during spontaneous respiration and the three other experiments were carried out under paced respiration. The rate of breathing was set by sound pulses of duration 0.5 s. The subject was asked to inhale when the sound signal appeared.

 

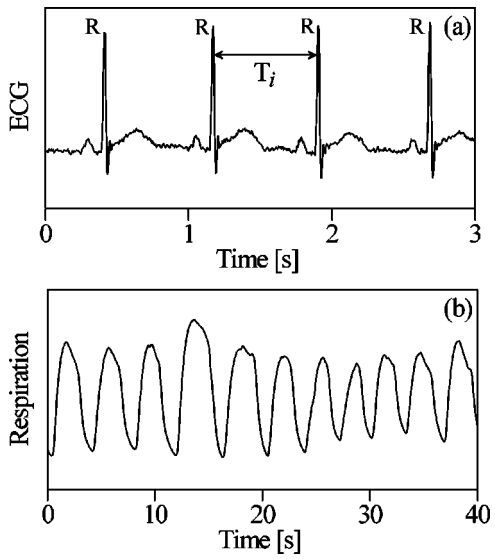


FIG. 1. Segments of an ECG signal (a) and of a respiratory signal (b) for the case of spontaneous breathing. Both signals are in arbitrary units.

There were no other requirements on the character of breathing. Each subject was suggested to choose himself the most comfortable duration of inhale and exhale and the amplitude of breathing. The frequency of paced respiration was fixed in two experiments (0.25 Hz and 0.1 Hz) and was linearly increasing from 0.05 Hz to 0.3 Hz in the third case. The duration of experiments under spontaneous breathing and fixed-frequency breathing was 10 min. Records under linearly changing frequency of respiration lasted 30 min. The subject was given 3–5 min to become accustomed to the required regime of respiration before measuring under fixed-frequency breathing. For one of the subjects a series of additional experiments was performed in the supine, sitting, and standing positions under spontaneous breathing. The duration of each of these measurements was 10 min.

Figure 1 shows short segments of a typical ECG and respiratory signals. There are several different ways for introducing phases for nonperiodic oscillations [25]. To calculate the phase of the ECG signal, following the usual convention, we assume that at the time moments $t_k$ corresponding to the appearance of $R$ peak (the highest and narrowest peak of the ECG attributed to the pumping action of the heart) the signal phase is increased by $2\pi$ [25]. Hence, we can assign to the times $t_k$ the values of the ECG signal phase $\phi_h(t_k)=2\pi k$, where $k=0,1,2,\ldots$. Such suggestion is relevant because the time interval between two subsequent $R$ peaks corresponds to one complete cycle of the oscillatory process and, therefore, the phase increase during this time interval is equal to $2\pi$. Within the interval between $R$ peaks the instantaneous phase is defined as follows:

$$\phi_h(t)=2\pi\frac{t-t_k}{t_{k+1}-t_k}+2\pi k, \quad t_k\leqslant t<t_{k+1}. \tag{1}$$

Defined in this way, the phase is a monotonically increasing piecewise-linear function of time and its computation does not require stationarity of the data. To calculate the respiratory signal phase $\phi_r$ we use the Hilbert transform [25] after removing low-frequency trend and high-frequency noise.

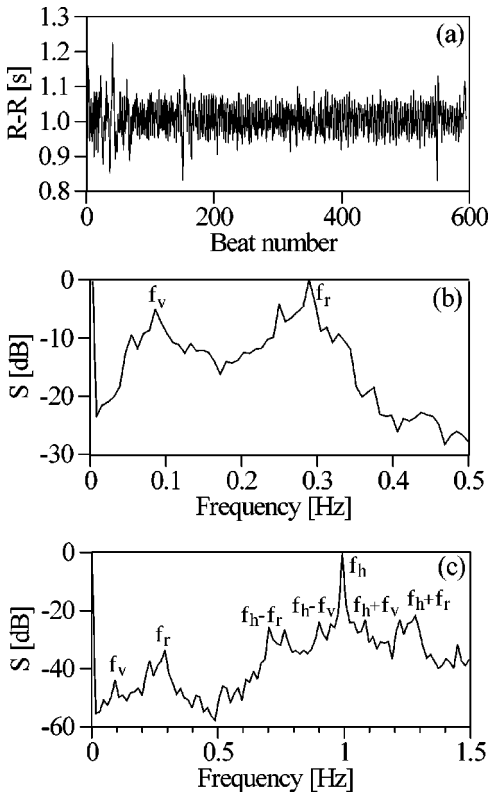


FIG. 2. Typical $R$-$R$ intervals (a) and their Fourier power spectra (b) and (c) calculated by different ways (see text); $f_h$ is the frequency of the main heart rhythm, $f_r$ is the respiratory frequency, and $f_v$ is the frequency of the process of slow regulation of blood pressure and heart rate.

Extracting from the ECG signals the sequence of $R$-$R$ intervals, i.e., the series of the time intervals $T_i$ between the two successive $R$ peaks, we obtain the information about the heart rate variability. Note that according to Ref. [26] the sampling frequency 250 Hz used in our experiments suffices to detect accurately the time moment of $R$ peak appearance. Typical sequence of $R$-$R$ intervals (tachogram) is shown in Fig. 2(a). To obtain equidistant time series from this not equidistant sequence we plot on the horizontal axis the time of $R$ peak appearance $t_k=\Sigma_{i=1}^{k}T_i$ instead of the beat number. Interpolating linearly this discrete dependence and resampling the resulting signal with a constant sampling time we obtain equidistant data to which the standard procedure of the Fourier power spectrum calculation can be applied.

The spectral analysis of $R$-$R$ intervals reveals different frequency domains of the HRV. Generally, the Fourier power spectrum of $R$-$R$ intervals demonstrates well-distinguished characteristic peaks at frequencies $f_r$ and $f_v$ associated with the respiratory and low-frequency fluctuations of the heart rate, respectively [Fig. 2(b)]. Besides high-frequency range, 0.15–0.4 Hz, and low-frequency range, 0.04–0.15 Hz, containing the peaks $f_r$ and $f_v$, respectively, a very low-frequency range, $<0.04$ Hz, is defined in the HRV power spectrum [26]. Physiological interpretation of the HRV spec-

trum components in the range $<0.04$ Hz warrants further elucidation [26]. This frequency domain is associated with humoral, vasomotion, and thermo regulations [27] or with metabolic and neurogenic processes [28], and it is not studied in this paper. It should be noted that the Fourier power spectra of *R-R* intervals and ECG signal are qualitatively the same if the first one is computed using a technique described in Ref. [22]. According to this technique, the original sequence of *R-R* intervals is presented as a sum of $\delta$ peaks placed at the time moments when *R* peaks occurred in the ECG. In this case the HRV power spectrum demonstrates peaks corresponding to the basic frequency $f_h$ of the heart rate and the combination frequencies $f_h \pm f_r$ and $f_h \pm f_v$ [Fig. 2(c)].

To separate the rhythm with frequency $f_v$ we filtered the sequence of *R-R* intervals removing the high-frequency fluctuations ($>0.15$ Hz) associated predominantly with respiration, i.e., RSA, and very low-frequency oscillations ($<0.05$ Hz). After this bandpass filtration we calculate the phase $\phi_v$ of the low-frequency heart rate fluctuations using the Hilbert transform and estimate the amplitude of MWSA as an average amplitude of the filtered signal oscillations. The validity of this way of the signal with frequency $f_v$ construction is demonstrated in Sec. IV.

To estimate the RSA amplitude we filtered the sequence of *R-R* intervals eliminating the low-frequency HRV and very low-frequency HRV. After that following the technique presented in Ref. [12], we compute the RSA amplitude for every respiratory cycle as the difference between the longest and the shortest *R-R* interval within this cycle and calculate the median of the distribution of the RSA amplitude for all respiratory cycles.

The intensity of the respiratory and low-frequency oscillations of the heart rate can also be measured from the HRV power spectrum [26]. It should be mentioned that at the breathing frequencies close to 0.1 Hz the power spectrum of *R-R* intervals demonstrates the only one well-distinguished peak at the frequency of breathing. Therefore, the estimation of the HRV intensity contains the contribution of both RSA and MWSA.

To detect synchronization between two signals we calculate the phase difference

$$\varphi_{n,m}^{12} = n\phi_1 - m\phi_2, \tag{2}$$

where $\phi_1$ and $\phi_2$ are the phases of the two signals, $n$ and $m$ are integers, and $\varphi_{n,m}^{12}$ is the generalized phase difference or relative phase [29]. The presence of $n:m$ phase synchronization is defined by the condition $|\varphi_{n,m}^{12} - C| < \text{const}$, where $C$ is a constant. In this case the relative phase difference $\varphi_{n,m}^{12}$ fluctuates around a constant value. Phase synchronization in noisy systems can be understood in a statistical sense as the appearance of a peak in the distribution of the cyclic relative phase [29]

$$\Psi_{n,m}^{12} = \varphi_{n,m}^{12} \bmod 2\pi. \tag{3}$$

Another technique widely used for the detection of synchronization between two signals is based on the analysis of the ratio of instantaneous frequencies $f_1/f_2$ of these signals. To compute the instantaneous frequencies we use the method described in Ref. [12]. Following this method we construct a local polynomial approximation for the instantaneous phase $\phi(t)$ on an interval essentially larger than the characteristic period of oscillations. A derivative of that polynomial function gives an estimate of the frequency of oscillations. In the region of frequency synchronization the ratio of frequencies of noisy signals remains approximately constant. The analysis of the instantaneous frequency ratio is usually used in addition to the analysis of phase differences. To compute the ratio $f_1/f_2$ there is no need to search for appropriate values of $n$ and $m$. Moreover, an approximately constant value of the ratio can be used for estimation of these integers.

The presence of synchronization between two signals can be demonstrated by plotting a synchrogram. To construct a synchrogram [12] we determine the phase $\phi_2$ of the slow signal at times $t_j$ when the cyclic phase of the fast signal attains a certain fixed value $\theta$, $\phi_1(t_j) \bmod 2\pi = \theta$, and plot $\psi_m^{12}(t_j)$ versus $t_j$, where

TABLE I. Summary of the experimental data for the case of spontaneous respiration. The subjects denoted by letters are listed in the order of increasing amplitude of respiratory sinus arrhythmia $A_{RSA}$. The main heart rhythm, respiration, and the process of low-frequency regulation of the heart rate are denoted as rhythms I, II, and III, respectively. $T_h$, $T_r$, and $T_v$ are the mean values of periods of the cardiac cycle, respiratory cycle, and low-frequency oscillations of the heart rate, respectively; $\sigma_h$, $\sigma_r$, and $\sigma_v$ are the standard deviations of respective periods. The amplitudes of RSA and MWSA are characterized by the mean values $A_{RSA}$ and $A_{MWSA}$ and by the standard deviations $\sigma_{RSA}$ and $\sigma_{MWSA}$, respectively.

| | Rhythm I (s) | | Rhythm II (s) | | Rhythm III (s) | | RSA (s) | | MWSA (s) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Code | $T_h$ | $\sigma_h$ | $T_r$ | $\sigma_r$ | $T_v$ | $\sigma_v$ | $A_{RSA}$ | $\sigma_{RSA}$ | $A_{MWSA}$ | $\sigma_{MWSA}$ |
| A | 0.68 | 0.02 | 2.96 | 0.26 | 10.64 | 2.54 | 0.02 | 0.01 | 0.02 | 0.01 |
| B | 0.61 | 0.03 | 3.17 | 0.37 | 9.33 | 1.89 | 0.04 | 0.01 | 0.03 | 0.02 |
| C | 0.81 | 0.05 | 2.96 | 0.45 | 10.31 | 2.80 | 0.05 | 0.02 | 0.06 | 0.03 |
| D | 0.74 | 0.04 | 3.12 | 0.37 | 9.85 | 1.56 | 0.06 | 0.02 | 0.07 | 0.03 |
| E | 0.88 | 0.07 | 3.70 | 0.70 | 9.80 | 2.35 | 0.08 | 0.04 | 0.06 | 0.04 |
| F | 0.90 | 0.06 | 4.02 | 0.47 | 9.35 | 1.46 | 0.09 | 0.03 | 0.08 | 0.05 |
| G | 0.74 | 0.19 | 3.83 | 0.77 | 9.19 | 2.11 | 0.25 | 0.19 | 0.21 | 0.11 |

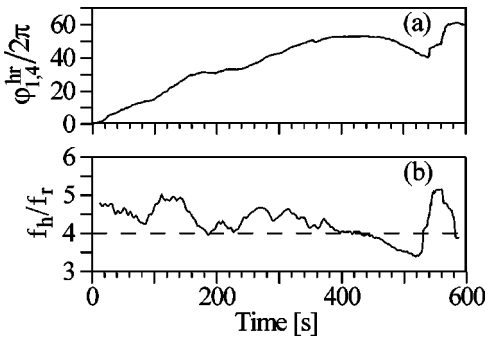


FIG. 3. Generalized phase difference $\varphi^{hr}_{1,4}$ (a) and the instantaneous frequency ratio (b) of the signals of ECG and spontaneous respiration for subject D, demonstrating 1:4 synchronization when four heartbeats occur within one respiratory cycle.

$$\psi^{12}_m(t_j) = \frac{1}{2\pi}[\phi_2(t_j) \bmod 2\pi m] \tag{4}$$

and $m$ is a number of adjacent cycles of the slow signal. In the case of $n{:}m$ synchronization, $\psi^{12}_m(t_j)$ attains only $n$ different values within $m$ adjacent cycles of the slow signal, and the synchrogram consists of $n$ horizontal lines.

To characterize the degree of synchronization between signals various synchronization measures have been proposed [29–31]. Analyzing the relative phases $\varphi^{12}_{n,m}$ we calculate the phase synchronization index

$$\gamma^{12}_{n,m} = |\langle \exp[i\varphi^{12}_{n,m}(t)]\rangle_t| = \sqrt{\langle \cos\varphi^{12}_{n,m}(t)\rangle^2_t + \langle \sin\varphi^{12}_{n,m}(t)\rangle^2_t}, \tag{5}$$

where angular brackets denote average over time [31]. By construction, $\gamma^{12}_{n,m}=0$ if the phases are not synchronized at all and $\gamma^{12}_{n,m}=1$ when the phase difference is constant (perfect synchronization).

## III. RESULTS

In this section we consider whether the interaction between the main rhythmic processes with frequencies $f_h$, $f_r$, and $f_v$ within the human cardiovascular system leads to their synchronization.

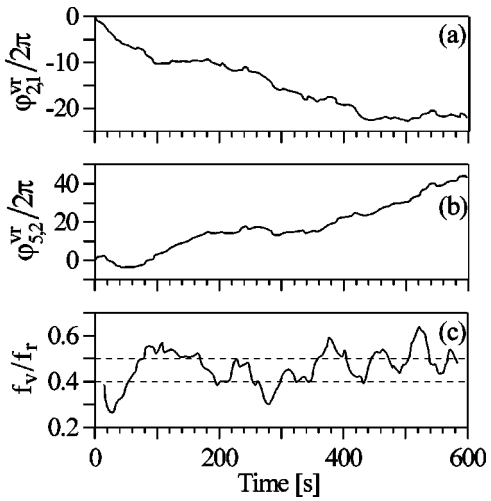


FIG. 4. Generalized phase differences $\varphi^{vr}_{2,1}$ (a) and $\varphi^{vr}_{5,2}$ (b) and the instantaneous frequency ratio (c) of the signal with basic frequency $f_v \approx 0.1$ Hz and the signal of spontaneous respiration with average frequency $f_r \approx 0.25$ Hz for subject F.

### A. Case of spontaneous respiration

The experimental data for the case of spontaneous breathing are presented in Table I. The table contains the mean values and standard deviations of periods of three main rhythms within the CVS. The subjects are listed in the order of ascending intensity of RSA.

Phase synchronization between the main heart rhythm and respiration has been demonstrated by several groups of investigators [12–14]. In our experiments we also observed synchronization between these rhythms lasting 30 s or longer for each of the seven subject studied. The duration of the longest epoch of synchronization within a 10-min record has been about 2 min. Almost all subjects demonstrated the presence of several different $n{:}m$ epoch of synchronization within one record.

Figure 3(a) shows the generalized phase difference $\varphi^{hr}_{1,4}$ between the ECG and respiratory signals calculated with Eq. (2), where $\phi_1=\phi_h$ is the ECG signal phase, $\phi_2=\phi_r$ is the phase of the respiratory signal, and $n=1$, $m=4$. One can see a horizontal plateau within the time interval 380–460 s indicating the presence of 1:4 phase synchronization between

TABLE II. Orders of synchronization detected between the rhythm with period $T_v$ and spontaneous respiration. The subjects denoted by letters are listed in the order of ascending amplitude of RSA. The synchronization regimes lasting 50 s or longer are presented. In the case of several epochs of synchronization of the same order the duration of the longest epoch is indicated.

| Code | Synchronization |
|---|---|
| A | 3:1 (55 s), 4:1 (170 s), 5:1 (50 s), 7:2 (100 s), 9:2 (50 s) |
| B | 3:1 (120 s), 5:2 (50 s), 7:2 (90 s), 10:3 (150 s) |
| C | 3:1 (70 s), 4:1 (125 s), 7:2 (50 s) |
| D | 3:1 (130 s), 5:2 (60 s) |
| E | 2:1 (90 s), 3:1 (180 s), 4:1 (60 s), 5:2 (130 s), 7:3 (70 s) |
| F | 2:1 (160 s), 5:2 (60 s), 7:3 (50 s) |
| G | 2:1 (145 s), 3:1 (80 s), 5:2 (70 s) |

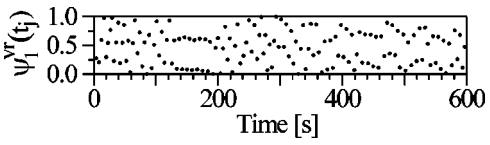


FIG. 5. Synchrogram demonstrating 2:1 synchronization for subject F under spontaneous respiration.

the cardiac and respiratory rhythms. Figure 3(b) illustrates the ratio of instantaneous frequencies of the heartbeat and breathing. Between 400 and 440 s the frequency ratio is practically constant, $f_h/f_r=4$, indicating frequency synchronization.

We have not found that cardiorespiratory synchronization tends to become weaker with increasing intensity of HRV as was reported in Refs. [9,13,24]. However, the number of subjects studied in our research is not sufficiently large to reveal statistical regularities.

To investigate a phase synchronization between the rhythm with frequency $\sim 0.1$ Hz and respiration, let us consider the phase difference $\varphi_{n,m}^{vr}$ calculated with Eq. (2), where $\phi_1=\phi_v$ is the phase of low-frequency oscillations of the heart rate computed after filtration of *R-R* intervals (Sec. II), and $\phi_2=\phi_r$. The analysis of the generalized phase difference $\varphi_{n,m}^{vr}$ and instantaneous frequency ratio $f_v/f_r$ indicates the presence of different $n:m$ epoch of synchronization, Table II.

Figure 4 illustrates 2:1 synchronization, when two adjacent respiratory cycles contain one cycle of low-frequency oscillations of the heart rate, and 5:2 synchronization. The generalized phase differences $\varphi_{2,1}^{vr}$ and $\varphi_{5,2}^{vr}$ normalized by $2\pi$ [Figs. 4(a) and (b)] exhibit plateaus within the time intervals 100–180 s and 180–240 s, respectively, indicating the presence of phase synchronization of orders 2:1 and 5:2, respectively. The instantaneous frequency ratio $f_v/f_r$ [Fig. 4(c)] is almost constant within approximately the same time intervals, indicating the presence of frequency synchronization also.

In Fig. 5 a synchrogram is shown. The presence of two almost horizontal lines in the plot of $\psi_1^{vr}(t_j)$ within the time interval 135–180 s confirms the presence of 2:1 locking illustrated by Fig. 4. Note that the distribution of the cyclic relative phase $\Psi_{2,1}^{vr}$ has a clear maximum within this time interval, indicating the presence of phase synchronization. High values of the phase synchronization index $\gamma_{2,1}^{vr}$ (Fig. 6) in the same interval also give an indication of phase synchronization.

During the last 160 s the relative phase $\varphi_{2,1}^{vr}$ [Fig. 4(a)] and the instantaneous frequency ratio $f_v/f_r$ [Fig. 4(b)] fluctuate in a more wide range than between 100 and 180 s, but these fluctuations take place around a constant value (on average, the frequency ratio $f_v/f_r\approx 0.5$). The plot of $\psi_1^{vr}(t_j)$ shows a two-band structure within this time interval, but these bands are not horizontal (Fig. 5). Nevertheless, the occurrence of two bands indicates that, on average, one cycle of low-frequency oscillations of the heart rate occurs within two respiratory cycles. Thus, the interval 440–600 s represents frequency locking.

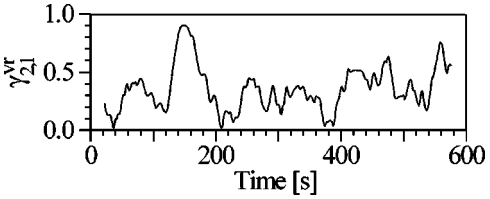


FIG. 6. Time evolution of the phase synchronization index $\gamma_{2,1}^{vr}$ for subject F under spontaneous respiration.

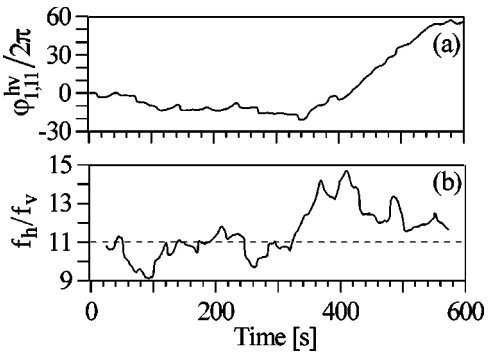


FIG. 7. Generalized phase difference $\varphi_{1,11}^{hv}$ (a) and the instantaneous frequency ratio (b) of the main heart rhythm and the rhythm with basic period $T_v$ for subject E under spontaneous respiration.

Studying synchronization between the process with frequency $f_v$ and respiration we have not revealed any relationship between the degree of synchronization and the intensities of RSA and MWSA (see Tables I and II) as well as in the case of cardiorespiratory synchronization. To investigate more thoroughly the influence of RSA and MWSA intensity on the degree of synchronization between the main rhythmic processes within the cardiovascular system we conducted a series of additional experiments. During these experiments the ECG and respiratory signals of subject D were recorded in the supine, sitting, and standing positions under spontaneous breathing. The intensities of RSA and MWSA are substantially different in various positions of a subject [26]. In our experiments we estimate the RSA amplitude as 0.10 s, 0.07 s, and 0.05 s, and the MWSA amplitude as 0.03 s, 0.06 s, and 0.08 s for the supine, sitting, and standing positions, respectively. However, the duration of epochs of synchronization between the main rhythms within the CVS and the number of the observed orders of synchronization were approximately similar for different positions of the subject.

Let us consider now whether the interaction of two self-oscillating processes, namely, the main heart rhythm with frequency $f_h$ and the process of blood pressure and heart rate regulation with frequency $f_v$, leads to their synchronization. Using Eq. (2) with $\phi_1=\phi_h$ and $\phi_2=\phi_v$ we calculate the phase difference $\varphi_{n,m}^{hv}$ and investigate its temporal behavior. We observe the regions where the relative phase $\varphi_{n,m}^{hv}$ fluctuates around a constant value [Fig. 7(a)]. However, on average, the duration of these epochs is shorter and the fluctuations of the relative phase within them are greater than in the cases considered above of synchronization between each of these rhythms and respiration. On the one hand, it can be a manifestation of some specific features of interaction between two physiological processes under investigation. On

the other hand, the ratio of the rhythms average frequencies $f_h$ and $f_v$ is significantly greater than the ratio of the frequencies $f_h$ and $f_r$, or $f_r$ and $f_v$. Therefore, the relatively small frequency fluctuation of one of the rhythms results in different number of cycles of the fast process within adjacent cycles of the slow process. As the result, $\varphi_{n,m}^{hv}$ exhibits phase slips and the regions of phase synchronization of close orders, for example, 1:10 and 1:11, are overlapped.

In Fig. 7(a) the generalized phase difference $\varphi_{1,11}^{hv}$ normalized by $2\pi$ is shown. Between 110 and 260 s, $\varphi_{1,11}^{hv}$ fluctuates around a constant value. The distribution of the cyclic relative phase $\Psi_{1,11}^{hv}$ has a pronounced maximum in this time interval, indicating the presence of phase synchronization in the statistical sense. The instantaneous frequency ratio $f_h/f_v$ [Fig. 7(b)] also fluctuates around a constant value within approximately the same time interval, so that, on average, the frequency ratio is close to 11. Besides 1:11 synchronization, we observe synchronization of other orders lasting longer than 5 cycle of the slow rhythm oscillations, i.e., having a duration over 50 s. However, we observe synchronization between the rhythmic processes with periods $T_h$ and $T_v$ only for 5 subjects (B, D, E, F, G).

### B. Case of paced respiration with a fixed frequency

Cardiorespiratory synchronization under paced respiration with a fixed frequency has been studied in Refs. [11,15,22]. For the case of breathing with the fixed frequency of 0.25 Hz we obtain the results coinciding qualitatively with those obtained for the above case of spontaneous respiration. We observe phase synchronization between the three main rhythmic processes operating within the CVS. In comparison with the case of spontaneous respiration the case of fixed-frequency breathing at 0.25 Hz is characterized by longer epochs of phase locking and higher index of phase synchronization. Probably, it is explained by the fact that the variability of fixed-frequency respiration is several times smaller than the variability of spontaneous respiration.

The case of breathing with the fixed frequency of 0.1 Hz is more specific. The power spectrum of *R-R* intervals demonstrates the only one well-distinguished peak at the frequency of breathing for all the subjects. To distinguish separately the contribution of RSA and MWSA to the heart rate variability is not possible in this case. The HRV amplitude under fixed-frequency breathing at 0.1 Hz is four to five times greater than the amplitudes of RSA and MWSA at frequencies of respiration far from 0.1 Hz. Thus, the signal of respiration, which can be regarded as an external force applied to the system generating oscillations with basic frequency $f_v$, leads to the resonant increasing of the HRV amplitude at this frequency, if the frequency of respiration is close to $f_v$.

Under paced respiration with the fixed period of 10 s we observe 1:1 phase and frequency synchronization between the variation of the heart rhythm and respiration during the entire record (Fig. 8). The time series of both respiration and *R-R* intervals are filtered with a bandpass 0.05–0.15 Hz. The phase synchronization index $\gamma_{1,1}^{vr}$ is close to unity within the entire interval of observation. Phase synchronization between the main heart rhythm and both the respiration and variation of *R-R* intervals is also observed. These two kinds of synchronization have the same orders.

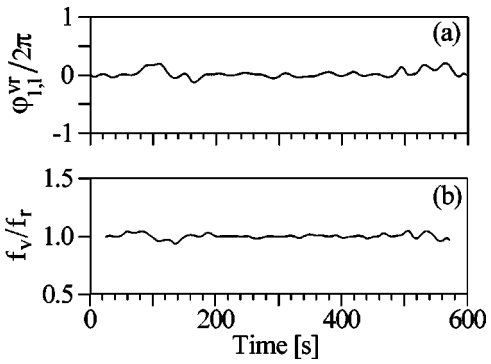


FIG. 8. Generalized phase difference $\varphi_{1,1}^{vr}$ (a) and the instantaneous frequency ratio (b) of the heart rate variation and respiration for subject D under fixed-frequency breathing at 0.1 Hz.

### C. Case of paced respiration with linearly increasing frequency

As far as we know, the interaction between various rhythms operating within the CVS has not been studied yet under paced respiration with linearly increasing frequency. The cardiorespiratory synchronization under paced respiration has been studied in detail in Ref. [15] for the respiratory frequencies from 3 to 30 breaths per min. However, during each 3-min measurement the subjects were breathing with a fixed frequency, and the respiratory frequency was increased by 1 breath per min from measurement to measurement. In our experiment the signals were recorded continuously during 30 min under respiratory frequency increasing linearly from 0.05 Hz to 0.3 Hz. Such a regime of breathing allows us to reduce substantially the total duration of the experiment directed to investigation of synchronization regime dependence on the respiratory frequency. Besides, the boundaries of synchronization regions can be defined more accurately during the continuous experiment because the step of frequency variation and variability of the human CVS intrinsic parameters are much less in this case than during the series of separate measurements under various breathing frequencies.

For each subject we observe various orders of synchronization between the main heart rhythm and respiration. For instance, subject F demonstrates cardiorespiratory synchronization of orders $1{:}m$, $m=5,6,\ldots,12$, lasting 5 cycle of respiration, or longer. Note that synchronization orders at low frequencies of breathing are higher than those at high frequencies. The results obtained in our study agree well with the results reported in Ref. [15]. They testify that the system generating the main heart rhythm can be treated as a generator in a physical sense, and that the respiration can be regarded as an external forcing of this system.

Figure 9 illustrates the case of 1:6 synchronization. A horizontal plateau in the range 1100–1300 s ($f_r \approx 0.20$–$0.23$ Hz) in the plot of the relative phase $\varphi_{1,6}^{hr}$ indicates the presence of phase synchronization. The phase syn-

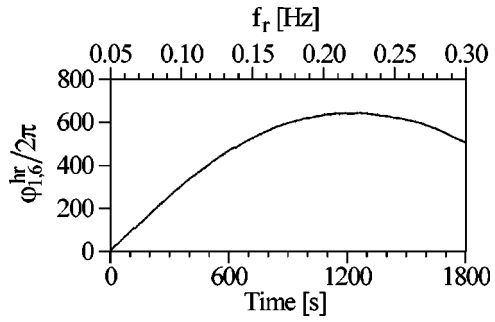


FIG. 9. Generalized phase difference $\varphi^{hr}_{1,6}$ of the signals of ECG and respiration for subject D under paced respiration with linearly increasing frequency $f_r$.

chronization index $\gamma^{hr}_{1,6}$ takes high values within this region and low values outside it.

Let us consider in detail the synchronization between the process whose basic frequency is $\sim$0.1 Hz and respiration. As in the previous case, the signal of respiration can be regarded as an external forcing applied now to the system generating self-sustained oscillations with frequency $f_v$. For the respiratory frequencies far from 0.1 Hz, the power spectra of *R*-*R* intervals computed in 3-min intervals of the 30-min recording demonstrate two main peaks at the frequency $f_v$ and the average frequency of respiration within the 3-min interval. For the respiratory frequencies close to 0.1 Hz, the power spectra of *R*-*R* intervals demonstrate one main peak at the average frequency of respiration. Thus, if the frequency of the external forcing, i.e., the frequency of respiration, is close to the basic frequency of the system responsible for the slow regulation of blood pressure and heart rate, then the frequency locking takes place.

Figure 10 shows a typical dependence of the frequency of the slow heart rate oscillations on the frequency of respiration. In this plot $f_r$ is the frequency at which the main peak is observed in the power spectrum of the respiratory signal and $f_v$ is the frequency at which the appropriate peak is observed in the power spectrum of *R*-*R* intervals. The power spectra of both respiration and *R*-*R* intervals are computed in a 3-min running window. The presence of 1:1 frequency locking is clearly seen within the interval 0.07–0.14 Hz. One can also see the regions where the experimental points are located along dashed lines with a fixed-frequency ratio.

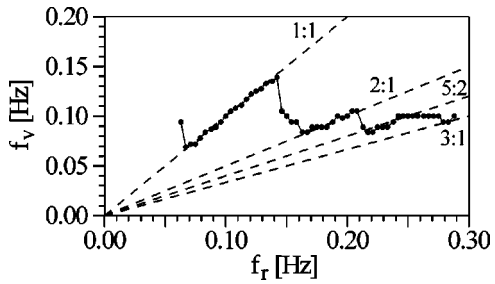


FIG. 10. Dependence of the frequency $f_v$ of the low-frequency heart rate oscillations on the respiratory frequency $f_r$ for subject D. Dashed lines are the lines along which the frequency ratio indicated by figures is constant.

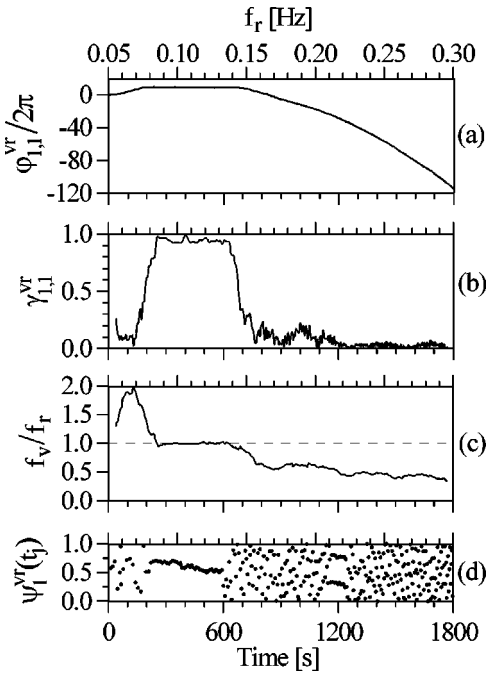


FIG. 11. Generalized phase difference $\varphi^{vr}_{1,1}$ (a), phase synchronization index $\gamma^{vr}_{1,1}$ (b), and the instantaneous frequency ratio (c) of the process of low-frequency regulation of heart rate and the process of respiration for subject B under linearly increasing frequency of respiration $f_r$. (d) Synchrogram, demonstrating one-band structure (1:1 synchronization) and two-band structure (2:1 synchronization).

These regions indicate the presence of frequency synchronization of order 2:1 in the interval $\approx$0.16–0.21 Hz and of order 5:2 in the interval $\approx$0.22–0.24 Hz.

The relative phase difference $\varphi^{vr}_{1,1}$ [Fig. 11(a)] exhibits plateau within the interval 200–650 s (0.08–0.14 Hz) indicating the presence of 1:1 phase synchronization. The phase synchronization index $\gamma^{vr}_{1,1}$ [Fig. 11(b)] is close to unity within the same interval and takes low values outside this interval. Figure 11(c) demonstrates the regions of frequency synchronization within which the instantaneous frequency ratio $f_v/f_r$ remains approximately constant. The interval of 1:1 phase locking is the longest one. The synchrogram [Fig. 11(d)] also gives indication of 1:1 and 2:1 synchronization under respiratory frequencies 0.08–0.13 Hz and 0.21–0.22 Hz, respectively. In these regions the synchrogram has a one-band and two-band structure, respectively.

Synchronization between the main heart rhythm and the rhythm with frequency $f_v$ is also observed under linearly increasing frequency of respiration. As well as in the cases of spontaneous breathing and fixed-frequency breathing, this kind of synchronization is less pronounced than the two others. We have not revealed any peculiarities of this kind of synchronization in comparison with experiments under another regimes of respiration.

## IV. DISCUSSION

It is well known that interaction between nonlinear oscillatory systems and biological oscillators in particular can

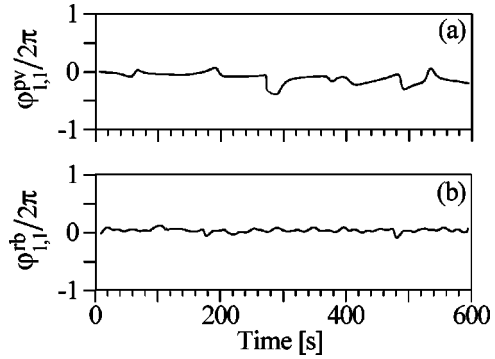


FIG. 12. (a) Generalized phase difference $\varphi^{pv}_{1,1}$ of the signal with basic frequency close to 0.1 Hz obtained from the time series of blood pressure and the signal with the same frequency constructed from the sequence of *R-R* intervals. (b) Generalized phase difference $\varphi^{rb}_{1,1}$ of the measured respiratory signal and the signal of breathing constructed from the sequence of *R-R* intervals.

result in their synchronization [1,32,33]. Investigations of signals of ECG, respiration, HRV, blood pressure, and blood flows testify the interaction between different rhythmic processes governing the cardiovascular dynamics in humans [28]. Our investigation shows that the interaction between the main rhythms operating within the CVS leads to their synchronization. The presence of epochs where the instantaneous frequency ratio of nonstationary signals remains stable while the frequencies themselves vary, and the existence of several different $n:m$ epochs within one record count in favor of the conclusion that the phenomena observed in our study are associated with the process of adjustment of rhythms of interacting systems.

To investigate synchronization between the three main rhythmic processes in the CVS, we have used in Sec. III only two experimentally measured signals, ECG and respiration. The signal with frequency of about 0.1 Hz associated with the blood pressure oscillations and low-frequency oscillations in the heart rate was obtained in the way described in Sec. II using filtration of the sequence of *R-R* intervals with the bandpass 0.05–0.15 Hz. To demonstrate the validity of this method of the signal with frequency $f_v$ construction we performed a series of additional experiments with two subjects in the sitting position under different regimes of breathing. During these experiments we simultaneously recorded three signals, namely, the ECG, respiration, and blood pressure on the middle finger of the right hand with the sampling frequency 250 Hz. After the blood pressure signal filtration with the bandpass 0.05–0.15 Hz we calculate the phase $\phi_p$ of this signal using the Hilbert transform. A typical phase difference $\varphi^{pv}_{1,1}=\phi_p-\phi_v$ for the case of fixed-frequency breathing at 0.25 Hz is shown in Fig. 12(a). The relative phase $\varphi^{pv}_{1,1}$ fluctuates around a constant value during the entire record indicating the presence of 1:1 phase synchronization between the signals with basic frequency close to 0.1 Hz obtained in different ways. Consequently, the results presented above for the rhythm with frequency $f_v$ separated from the sequence of *R-R* intervals qualitatively coincide with the results obtained using the time series of blood pressure.

Moreover, synchronization between the three main rhythms in the human cardiovascular system can be detected based on the analysis of univariate data, since the signal of respiration can be obtained from the HRV data as well as the signal of the low-frequency heart rate fluctuations. We filtered the sequence of *R-R* intervals with the bandpass 0.15–0.4 Hz and calculated the phase $\phi_b$ of this filtered signal. Then we compare the phase $\phi_b$ with the phase $\phi_r$ computed directly from the respiratory signal filtered with the same bandpass. The phase difference $\varphi^{rb}_{1,1}=\phi_r-\phi_b$ presented in Fig. 12(b) for the case of breathing at 0.25 Hz indicates the existence of 1:1 phase synchronization during the entire 10-min record. Thus, a respiratory signal constructed from the heart rate variability data exhibits similar synchronization as for the recorded respiratory signal. These results agree well with those presented in Refs. [14,22] where it has been shown that the presence or absence of phase synchronization between different interacting processes can be detected using univariate data.

The experiments with linearly increasing frequency of respiration clearly indicate that the system generating the rhythm associated with the low-frequency fluctuations of the heart rate can be regarded as a self-sustained oscillator under external forcing, affected by noise. The commonness of phenomena observed in periodically driven self-sustained oscillators of physiological and physical nature is demonstrated in Ref. [12]. It has been shown there that qualitatively the same features of phase and frequency synchronization are observed in the case of external forcing of the main heart rhythm by respiration and in the case of periodic driving of van der Pol oscillator in the presence of noise,

$$\ddot{x}-\mu(1-x^2)\dot{x}+\omega_0^2 x=\varepsilon\sin(vt)+\xi, \tag{6}$$

where $\mu$ is the parameter of nonlinearity, $\omega_0$ is the natural frequency, $\varepsilon$ and $v$ are, respectively, the amplitude and frequency of the external force, and $\xi$ is the Gaussian white noise. To demonstrate the 1:3 locking typical for the cardiorespiratory system, the frequency ratio $v/\omega_0$ has been chosen between 1/4 and 1/3 in Ref. [12]. As a result, the synchronization at subharmonic has been observed.

In the case of an external forcing of the oscillatory process with fundamental frequency $f_v\approx 0.1$ Hz by respiration, we can observe synchronization at the fundamental frequency and higher harmonics. In system (6) this situation corresponds to the cases $v/\omega_0\sim 1$ and $v/\omega_0>1$. The phase and frequency synchronization described in the preceding section is qualitatively similar to the one observed in system (6) under linearly increasing frequency of the external force. The phase difference $\varphi_{1,1}=\phi_{vdP}-vt$, where $\phi_{vdP}$ is the phase of the oscillator, is presented in Fig. 13(a). System (6) parameters are $\mu=1$, $f_0=\omega_0/2\pi=0.1$ Hz, $f_d=v_0/2\pi$ varies from 0.05 Hz to 0.3 Hz, $\varepsilon=0.45$, and $\xi$ has a zero mean and standard deviation of 3% of the standard deviation of the data without noise. Under driving frequencies of 0.08–0.15 Hz the 1:1 locking takes place with a horizontal plateau in the plot of $\varphi_{1,1}$ [Fig. 13(a)] and a clear one-band structure in the synchrogram [Fig. 13(b)]. This band in Fig. 13(b) is not horizontal but has a slope. This result agrees well with the

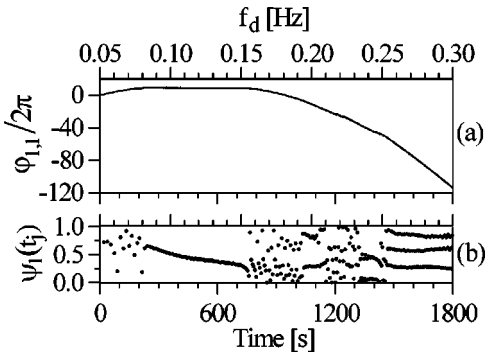


FIG. 13. (a) Generalized phase difference $\varphi_{1,1}$ of the van der Pol oscillator and the external force with linearly increasing frequency $f_d$. (b) Synchrogram demonstrating synchronization of orders 1:1 (one band), 2:1 (two bands), and 3:1 (three bands).

results of theoretical investigation of the oscillation phase dependence on the frequency detuning in the case of self-sustained oscillator synchronization at the fundamental frequency by external harmonic force [34]. Under driving frequencies of 0.25–0.3 Hz the 3:1 synchronization is observed with a three-band structure in Fig. 13(b). For the driving frequencies close to 0.2 Hz the synchrogram shows a short epoch with two distinct bands indicating that, on average, one cycle of oscillator occurs within two cycles of the external force. The qualitative similarity of Fig. 13 and Figs. 11(a) and (d) confirms the commonness of the obtained results. The 3:1 synchronization absent in Fig. 11(d) can be probably achieved at higher values of the respiratory frequency.

To describe mathematically the process of blood pressure and heart rate regulation with the frequency close to 0.1 Hz, on physiological grounds the models in the form of delay-differential equations have been proposed [35,36]. Applying a harmonic external forcing or forcing with linearly increasing frequency to these models, we observe that they demonstrate the phase and frequency locking qualitatively similar to the one described above for the experimental signals. These results also testify that the system generating the rhythm with the frequency of about 0.1 Hz in the human cardiovascular system can be regarded as a self-sustained oscillator.

## V. CONCLUSION

Analyzing the signals gained with the use of noninvasive methods we have shown that the three main rhythmic processes in the human cardiovascular system can be synchronized with each other. It has been found that synchronization between the main heart rhythm and the rhythm whose fundamental frequency is close to 0.1 Hz is less pronounced than synchronization between each of these rhythms and respiration. We observed synchronization between the respiration and the two other rhythms for each subject under various regimes of breathing. We have shown that phases of rhythms can be locked with different ratios $n:m$, and that the presence of several different orders of synchronization is typical for subjects studied. Under paced respiration with a fixed frequency or linearly increasing frequency, the synchronization between the main processes governing the CVS dynamics was stronger than synchronization in the case of spontaneous respiration. We have not revealed a relationship between the degree of synchronization and the intensities of respiratory sinus arrhythmia and Mayer wave sinus arrhythmia. The inter-relation between these phenomena needs further investigation.

In further research, we plan to detect synchronization between the main rhythmic processes operating within the human cardiovascular system from univariate data in the form of *R-R* intervals. It seems promising to compare the features of synchronization between the main rhythms in the cardiovascular system of healthy and sick humans and to investigate a possibility of using the obtained results for diagnostics of a human state.

## ACKNOWLEDGMENTS

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