Experimental Observation of Synchronization Between Rhythms of Cardiovascular System

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Synchronization between 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 is studied under different regimes of breathing. The analysis of the experimental records reveals synchronous regimes of different orders $n:m$ between all the three main rhythms. Investigation of the model system is carried out demonstrating a good qualitative coincidence with experimentally observed results.

Key words: synchronization, time series analysis, cardiovascular system, heart rate oscillations

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1 Introduction

The coexistence of rhythmic processes interacting with each other is typical for living organisms [1]. For example, operation of human cardiovascular system (CVS) is governed by the following most significant oscillating processes: 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 [2]. Recently, it has been found that the main heart rhythm and respiration can be synchronized [3–7]. The process with a frequency $f_v \approx 0.1$ Hz has been intensively studied [2,8-11]. However, the ability of this rhythm to become synchronized to the respiratory and cardiac rhythms with frequencies f_r and f_h, respectively, invites further investigation. Phase synchronization in statistical sense between the spontaneous respiration and the process whose period is about 10 s has been reported in [12]. Interaction between the main heart rhythm and the process with the frequency f_v has been studied mainly in terms of physiology [2,11] and in the models [9,13,14]. Note that the model proposed in [13] 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 two other rhythms (respiration and heartbeat) under different regimes of breathing. The paper is orga-

*The corresponding author for future communications nized as follows. In Section 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 and paced respiration. Section IV contains investigation of equations modelling slow oscillations in blood pressure. In Section V we summarize our results.

2 Data Processing Techniques

We studied 7 healthy volunteers. They were men aged 20–34 years. 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 three other experiments were carried out under paced respiration. Sound pulses set the rate 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 minutes. Records under linearly changing frequency of respiration lasted 30 minutes.

Figure 1 shows short segments of typical ECG and respiratory signals. 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 2π [15]. Hence, we can assign to the times t_k the values of the ECG signal phase $\phi_h(t_k) = 2\pi k$, where $k = 0, 1, 2, \ldots$. Within the interval between R peaks the instantaneous phase is defined as follows

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

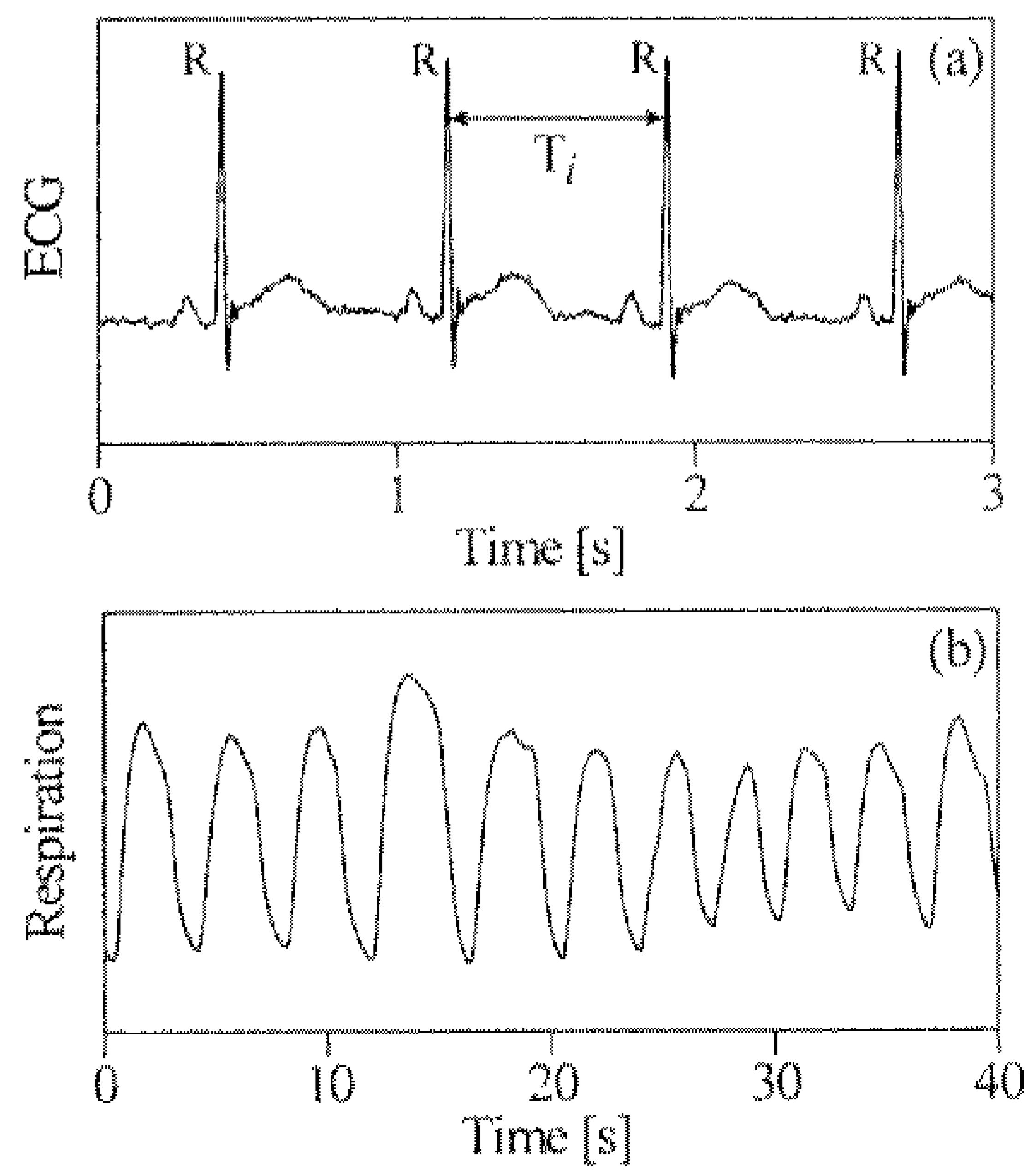

FIG. 1. Segments of an ECG signal (a) and of a respiratory signal (b) for the case of spontaneous breathing. Both signals are in arbitrary units.

To calculate the respiratory signal phase ϕ_r we use the Hilbert transform [15] after removing low-frequency trend and high-frequency noise.

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. Typical sequence of R-R intervals (tachogram) is shown in figure 2(a). To obtain equidistant time series from this not equidistant sequence we plot on the horizontal axis the time of R peak appearance $t_k = \sum_{i=1}^{k} T_i$ 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 [figure 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 fre-

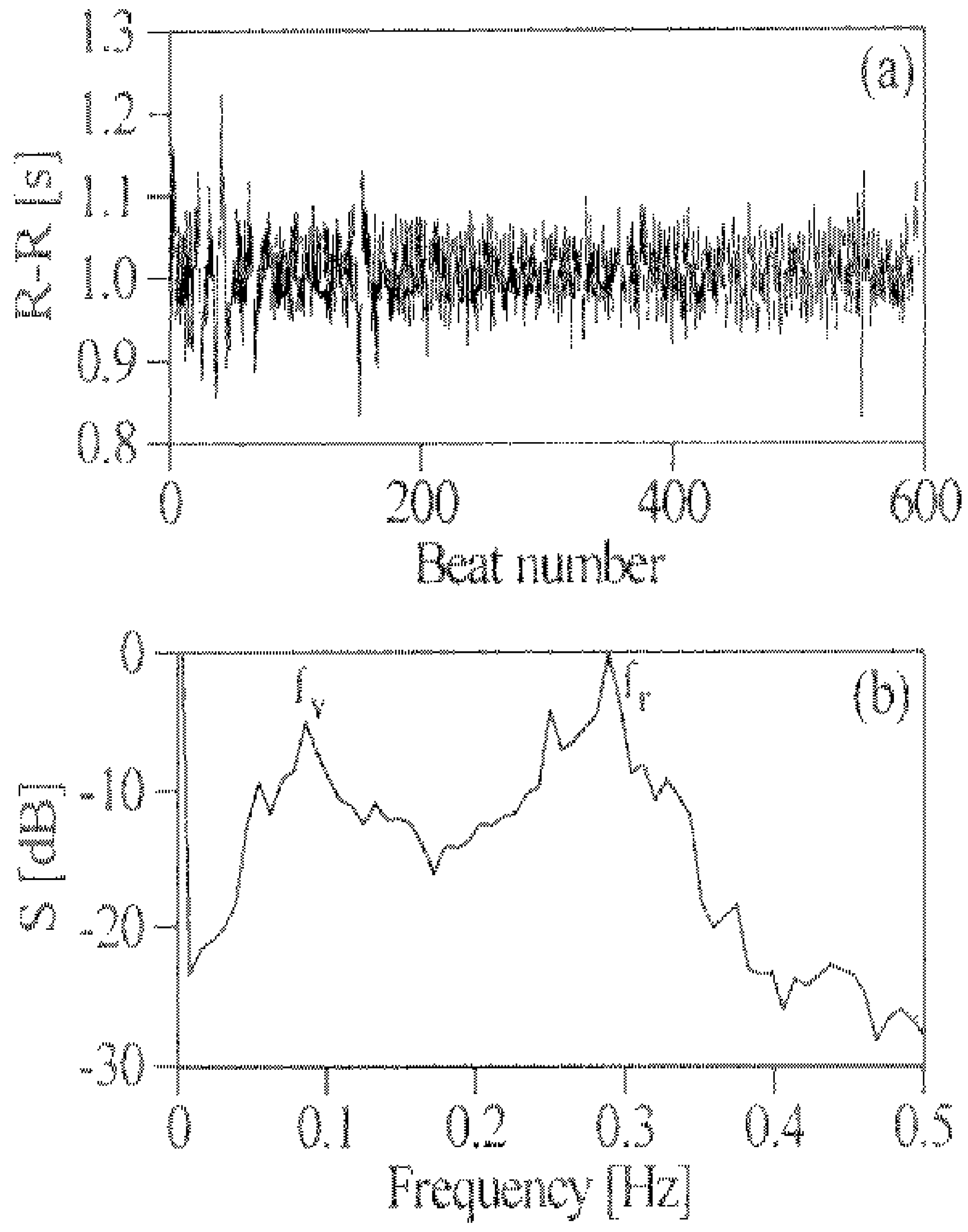

FIG. 2. Typical R-R intervals (a) and their Fourier power spectra (b)

quency range, < 0.04 Hz, is defined in the HRV power spectrum [16]. To separate the rhythm with frequency f_v we filtered the sequence of R-R intervals removing the high-frequency fluctuations (> 0.15 Hz) and very low frequency oscillations (< 0.05 Hz). After this bandpass filtration we calculate the phase ϕ_v of the low-frequency heart rate fluctuations using the Hilbert transform.

To detect synchronization between two signals we calculate the phase difference

$$\varphi_{n,m}^{12} = n\phi_1 - m\phi_2, \qquad (2)$$

where ϕ_1 and ϕ_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 [4]. The presence of n:m phase synchronization is defined by the condition $\left|\varphi_{n,m}^{12} - C\right| < const$, where C is a constant. In this case the relative phase difference $\varphi_{n,m}^{12}$ fluctuates around a constant value.

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 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 presence of synchronization between two signals can be demonstrated by plotting a synchrogram. To construct a synchrogram [4] we determine the phase ϕ_2 of the slow signal at times t_j when the cyclic phase of the fast signal attains a certain fixed value θ, $\phi_1(t_j) \bmod 2\pi = \theta$, and plot $\psi_m^{12}(t_j)$ versus t_j, where

$$\psi_m^{12}(t_j) = \frac{1}{2\pi}\left(\phi_2(t_j) \bmod 2\pi m\right) \qquad (3)$$

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

3 Experimental 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.

3.1 Synchronization between the rhythms under spontaneous respiration

Phase synchronization between the main heart rhythm and respiration has been demonstrated by several groups of investigators [4-6]. In our experiments we also observed synchronization between these rhythms lasting 30 s or longer for each of the seven subject studied. 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 $\varphi_{1,4}^{hr}$ between the ECG and respiratory signals calculated with Equation (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

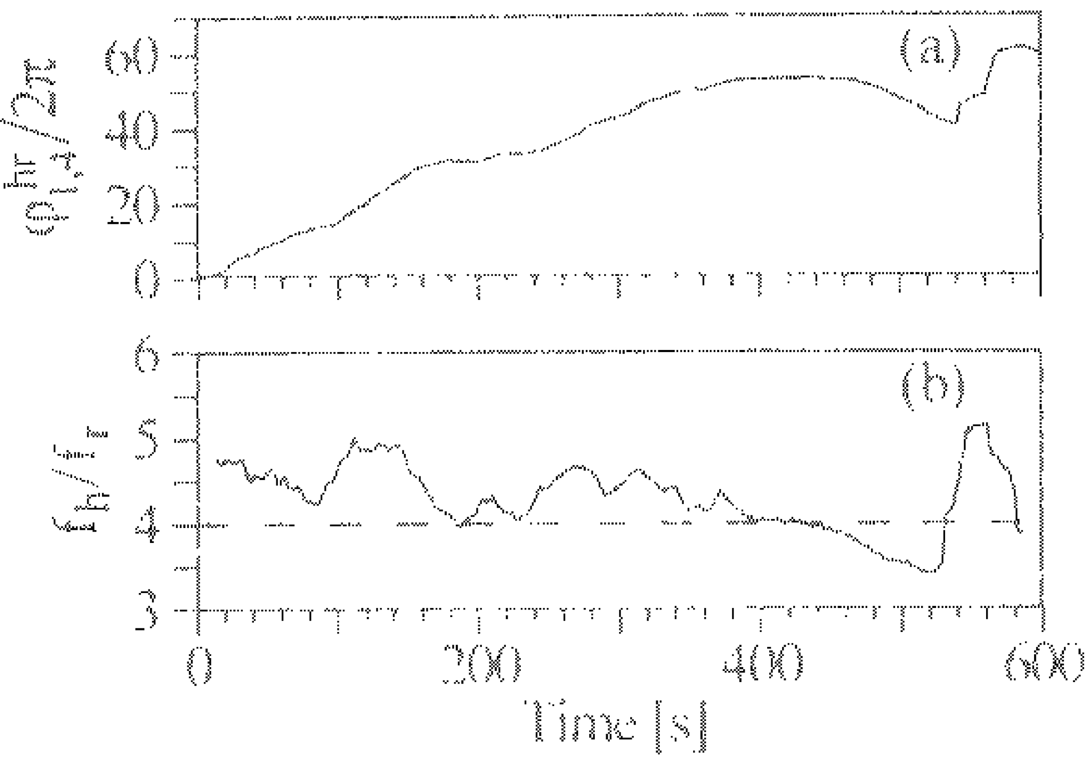

FIG. 3. Generalized phase difference $\varphi^{hr}_{1,4}$ (a) and the instantaneous frequency ratio (b) of the signals of ECG and spontaneous respiration, demonstrating 1:4 synchronization.

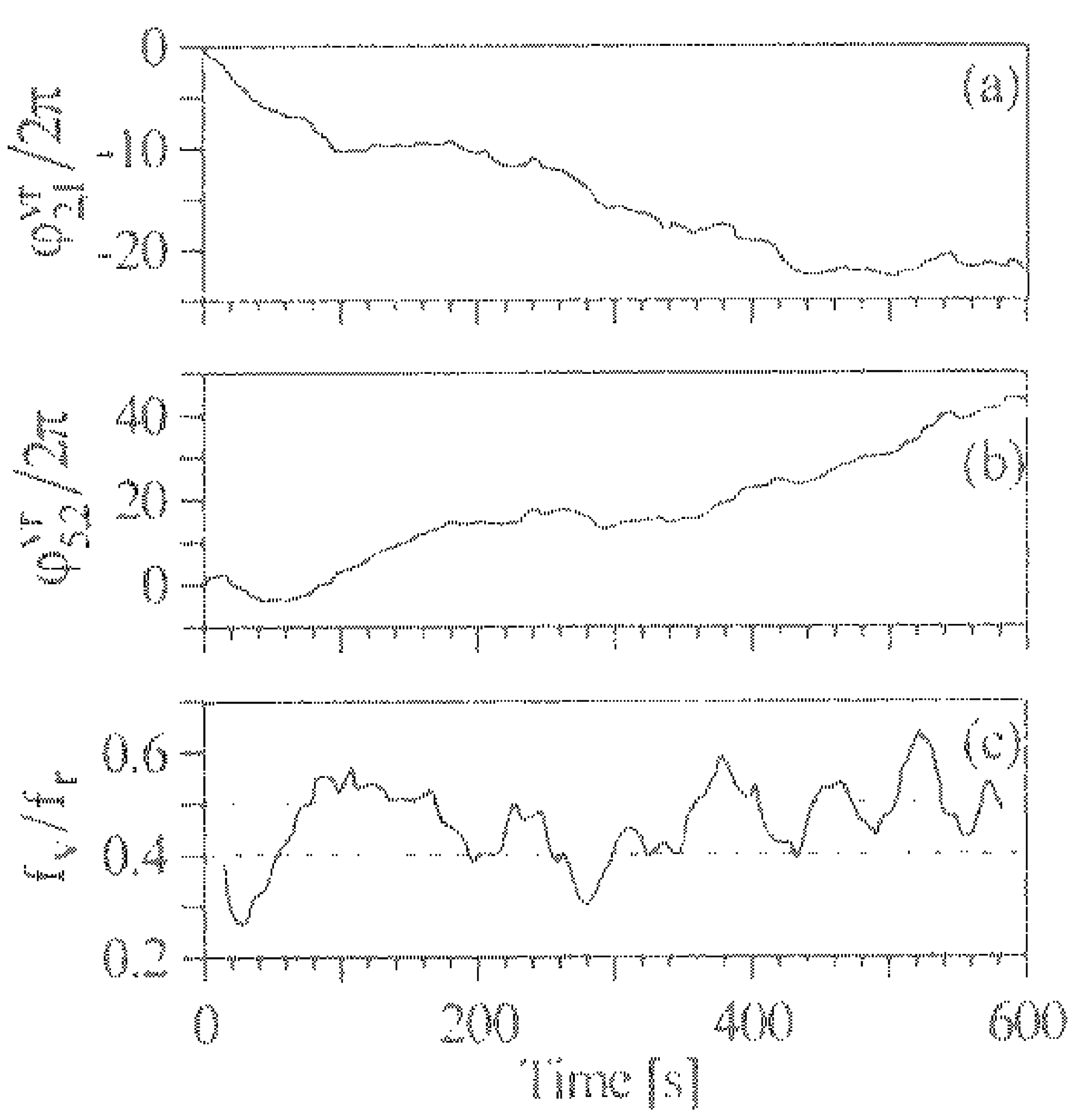

FIG. 4. Generalized phase differences $\phi^{vr}_{2,1}$(a)and $\phi^{vr}_{5,2}$(b) and the instantaneous frequency ratio (c) of the signal with basic frequency f_v and the signal of spontaneous respiration.

can see a horizontal plateau within the time interval 380–460 s indicating the presence of 1:4 phase synchronization between 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.

To investigate a phase synchronization between the rhythm with frequency ~ 0.1 Hz and respiration let us consider the phase difference $\varphi^{vr}_{n,m}$, where $\phi_1 = \phi_v$ is the phase of low-frequency oscillations of the heart rate, and $\phi_2 = \phi_r$. The analysis of the generalized phase difference $\varphi^{vr}_{n,m}$ and instantaneous frequency ratio f_v/f_r indicates the presence of different n:m epoch of synchronization, Table 1.

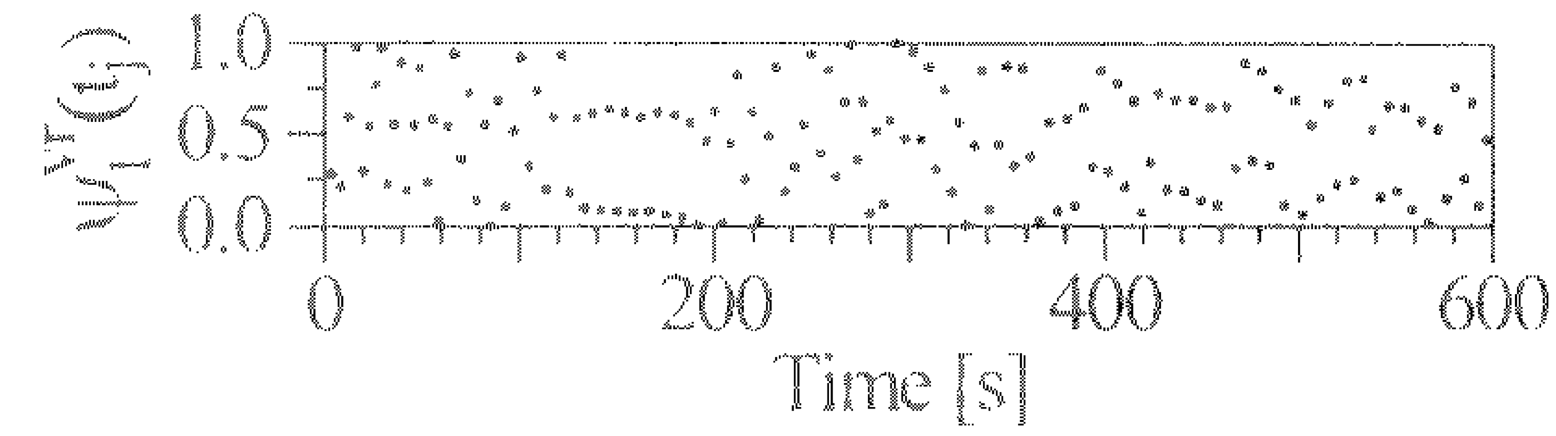

FIG. 5. Synchrogram demonstrating 2:1 synchronization for subject F under spontaneous respiration.

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 $\varphi^{vr}_{2,1}$ and $\varphi^{vr}_{5,2}$ normalized by 2π [figures 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 [figure 4(c)] is almost constant within approximately the same time intervals, indicating the presence of frequency synchronization also.

In figure 5 a synchrogram is shown. The presence of two almost horizontal lines in the plot of $\psi^{vr}_1(t_j)$ within the time interval 135–180 s confirms the presence of 2:1 locking illustrated by figure 4.

Let us consider now the interaction of two self-oscillating processes, namely, the main heart rhythm and the process of blood pressure and heart rate regulation. Using Equation (2) with $\phi_1 = \phi_h$ and $\phi_2 = \phi_v$ we calculate the phase difference $\varphi^{hv}_{n,m}$ and investigate its temporal behavior. We observe the regions where the relative phase $\varphi^{hv}_{n,m}$ fluctuates around a constant value. 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. There-

Table 1. Orders of synchronization detected between the rhythm with period T_v and spontaneous respiration. The subjects are denoted by letters. 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),
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)

fore, 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. We observe synchronization between the rhythmic processes with periods T_h and T_v only for 5 subjects (B, D, E, F, G).

3.2 Synchronization between the rhythms under paced respiration

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 this case of breathing is characterized by longer epochs of phase locking. 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. 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. The time series of both respiration and R-R intervals are filtered with a bandpass 0.05–0.15 Hz. 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.

In the case of linearly increasing frequency of respiration we observe various orders of synchronization between the main heart rhythm and respiration for each subject. For instance, subject F demonstrates cardiorespiratory synchronization of orders $1{:}m$, $m = 5, 6, \ldots, 12$, lasting 5 cycles of respiration, or longer. The results obtained in our study agree well with the results reported in [7]. 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 6 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 $\varphi^{hr}_{1,6}$ indicates the presence of phase synchronization.

Let us consider in detail the synchronization between the process whose basic frequency is ~ 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-minute intervals of the 30-minute recording demonstrate two main peaks at the frequency f_v and the average frequency of respiration within the 3-minute interval. For the respiratory frequencies close to 0.1 Hz the power spectra of R-R intervals demonstrate one main peak at the

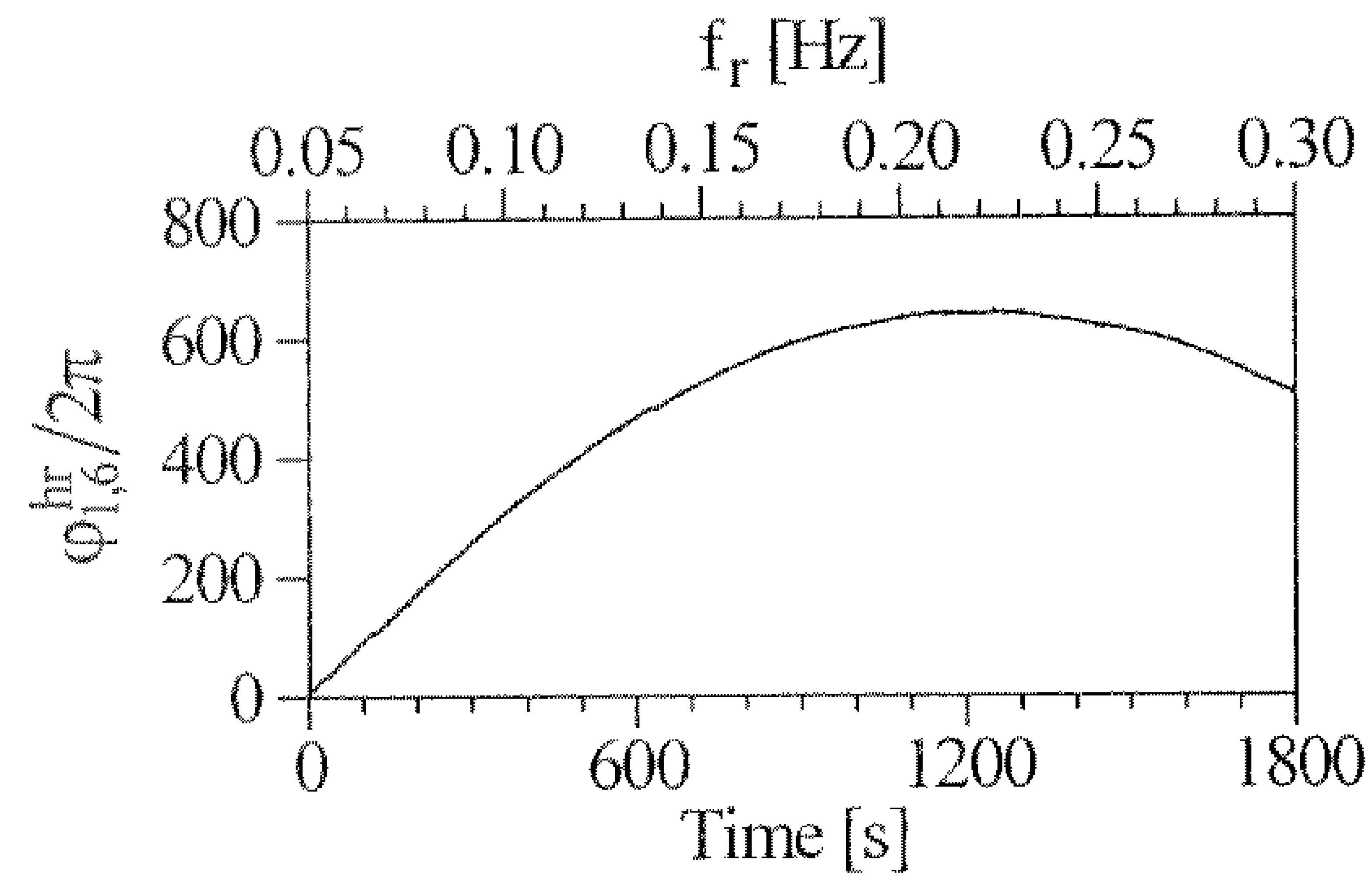

FIG. 6. Generalized phase difference of the signals of ECG and respiration under paced respiration with linearly increasing frequency.

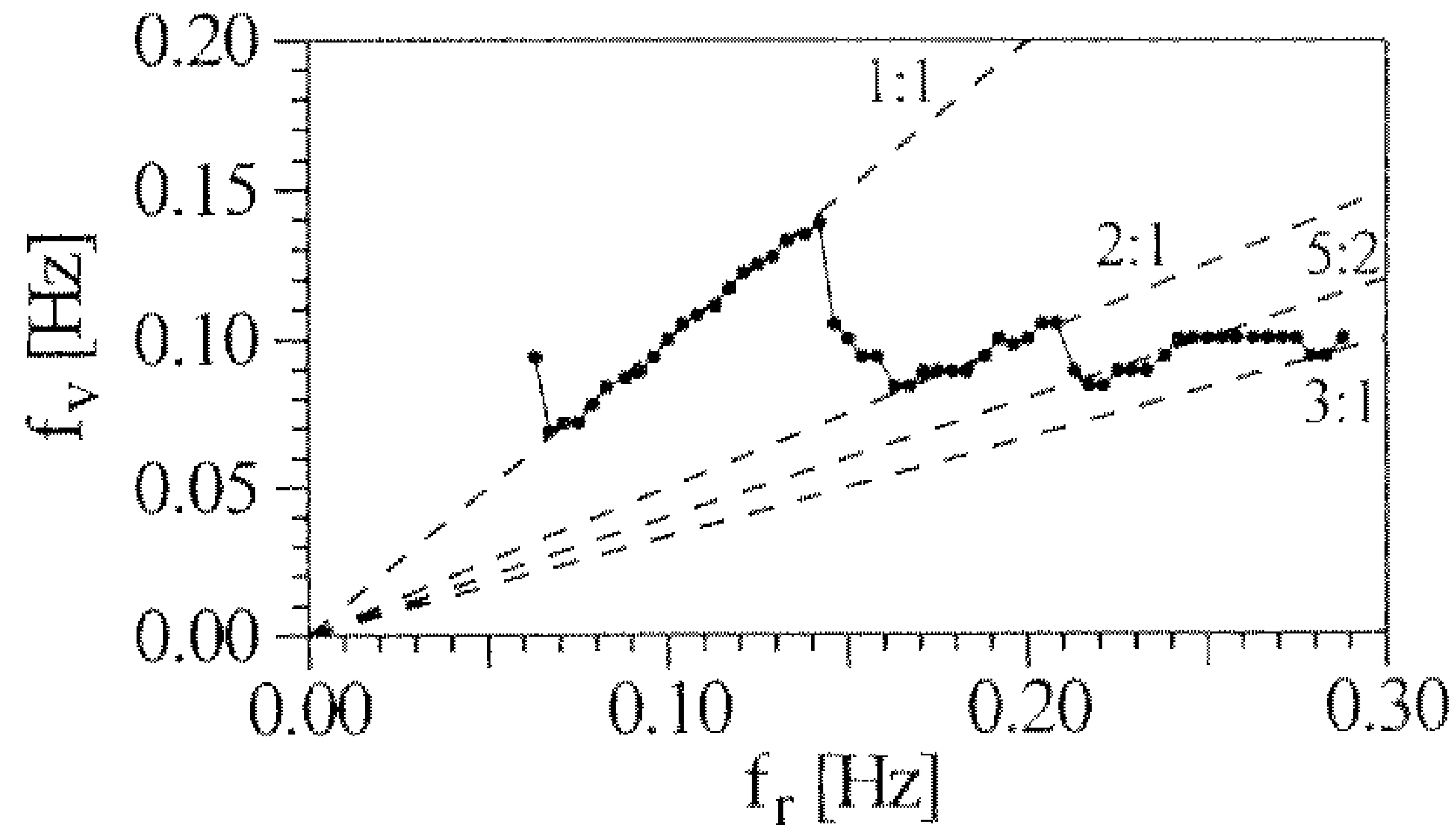

FIG. 7. Dependence of the frequency of the low-frequency heart rate oscillations f_v on the respiratory frequency f_r. Dashed lines are the lines along which the frequency ratio indicated by figures is constant.

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 7 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-minute 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. 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 $\varphi^{vr}_{1,1}$ [figure 8(a)] exhibits plateau within the interval 200–650 s (0.08–0.14 Hz) indicating the presence of 1:1 phase synchronization. Figure 8(b) 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 [figure 8(c)] 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.

4 Simulation results

To describe mathematically the process of blood pressure and heart rate regulation with the frequency close to 0.1Hz, on physiological grounds the models in the form of delay-differential equations have been proposed [17,18]. For example, the nonlinear feedback model considered in [18] can be written in the following form

$$\varepsilon \dot{x}(t) = -x(t) + f\left(x(t-\tau)\right), \qquad (4)$$

where x characterizes the mean arterial pressure, τ is the total delay time which is a sum of afferent and efferent delays, ε is the lag in vasculature dynamics, and function f defines nonlocal correlations in time. The function f has demonstrated a sigmoidal nonlinearity

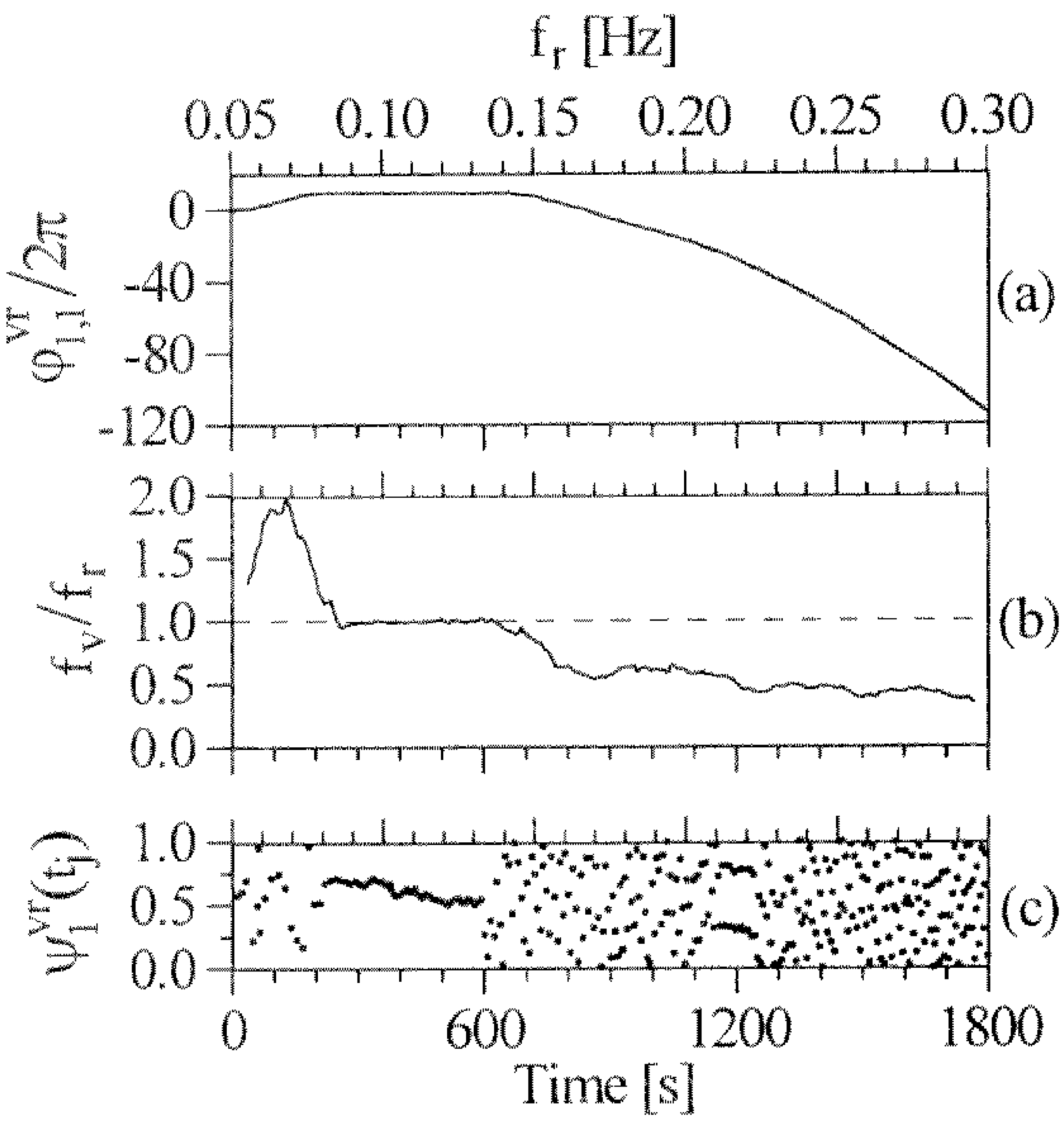

FIG. 8. Generalized phase difference (a), and the instantaneous frequency ratio (b) between the process of low-frequency regulation of the heart rate and the process of respiration under linearly increasing frequency of respiration. (c) Synchrogram, demonstrating one-band structure (1:1 synchronization) and two-band structure (2:1 synchronization).

$$f(x) = \frac{c}{(1 + a\exp[-b(x - x^*)])} - \frac{c}{(1 + a\exp[b(x - x^*)])}, \quad (5)$$

where the parameters a, b, c, and x^* specify the shape of the characteristic [18]. This model provides for sustained stable oscillations under a wide variety of parameter variations, i.e. physiological conditions.

Applying a harmonic external forcing or forcing with linearly increasing frequency to the model (4), we observe that it demonstrates the phase and frequency locking qualitatively similar to the one described above for experimental signals. In the case of periodic driving in the presence of noise the nonlinear feedback model (4) takes the form

$$\varepsilon\dot{x}(t) = -x(t) + f(x(t-\tau)) + A\sin(\nu t) + \xi, \quad (6)$$

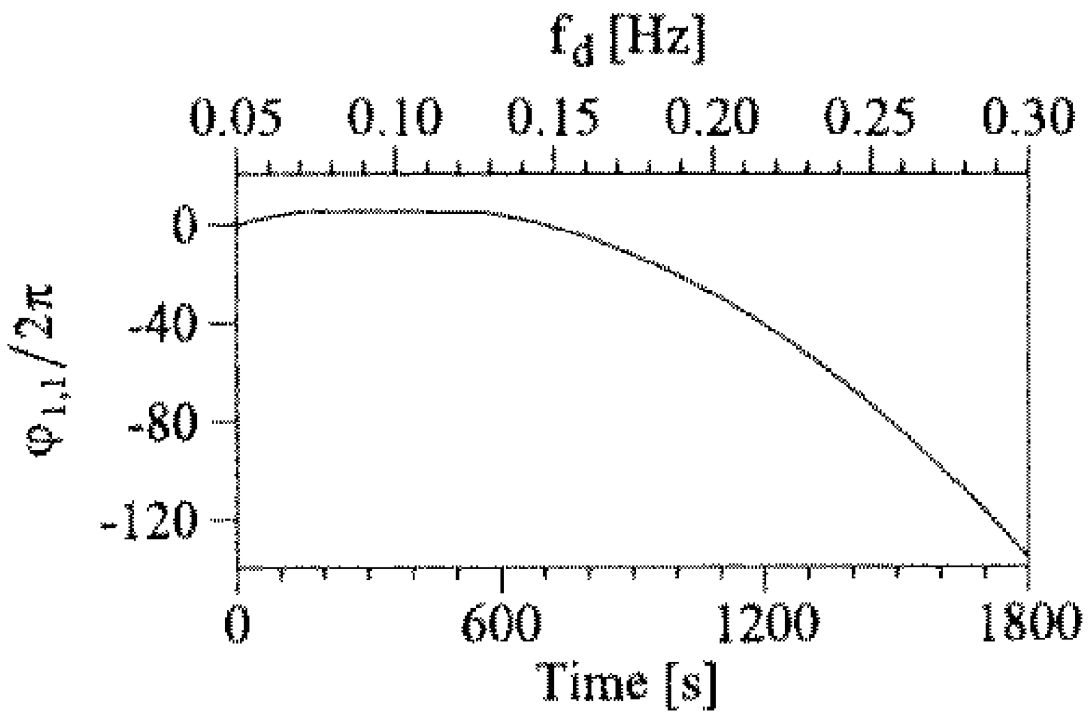

FIG. 9. Generalized phase difference $\varphi_{1,1}$ of the nonlinear feedback oscillator and the external force with linearly increasing frequency f_d.

where A and ν are respectively the amplitude and frequency of the external force, and ξ is the Gaussian white noise.

For the case of linearly increasing frequency of the external force the phase difference $\varphi_{1,1} = \phi_{osc} - \nu t$, where ϕ_{osc} is the phase of the oscillator (6), is presented in figure 9. The system parameters are chosen in according with recommendations given in [18]. We use $\tau = 4$ s, $\varepsilon = 1.3$ s, $a = 1$, $b = 2$, $c = 3.3$, $x* = 0.5$, $f_d = \nu/2\pi$ varies from 0.05 Hz to 0.3 Hz, $A = 1.4$, and ξ has a zero mean and standard deviation of 3% of the standard deviation of the data without noise. Under driving frequencies of 0.07 – 0.13 Hz the 1:1 locking takes place with a horizontal plateau in the plot of $\varphi_{1,1}$ (figure 9).

The qualitative similarity of figure 9 and figure 8(a) confirms the commonness of phenomena observed in the considered periodically driven oscillators of physiological nature. These results also testify that the system generating within the human cardiovascular system the rhythm with the frequency of about 0.1 Hz can be treated as a self-sustained oscillator.

5 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. 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. 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.

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.

Acknowledgments

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