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========== **MATHEMATICAL MODELING** ==========

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The role of hydrodynamic parameters in the forming of low-frequency oscillations in arterial blood pressure in human

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Abstract. The mechanism of forming of low-frequency oscillations in the human cardiovascular system is a burning issue today. The current paper considers a hypothesis of hydrodynamic nature of these oscillations, which are formed without the involvement of autonomous control of the cardiovascular system from the autonomic nervous system. The developed reduced hydrodynamic model was used to study the system response on additive periodic perturbation of wide-ranged frequencies that affects the performance of the heart pump, as well as the role of hydrodynamic parameters of the cardiovascular bed in this process. It was shown that low-frequency perturbation of pump wall rigidity forms low-frequency oscillations in the arterial part of the cardiovascular flow without autonomous control, with the maximum amplitude observed at frequency close to 0.1 Hz.

Key words: *cardiovascular system, pressure oscillations, blood flow oscillations, mathematical modeling.*

INTRODUCTION

Low-frequency oscillations of arterial blood pressure (ABP) of the human cardiovascular system (CVS), the so-called Mayer waves, have a period of 10 s (0.1 Hz) regardless of sex, age and body position [1]. It is supposed that baroreflex feedback loop, which exhibits resonance behavior at 0.1 Hz, is the main mechanism underlying the forming of such oscillations [1, 2]. This phenomenon is used for baroreflex stimulation in deep breathing with a frequency of 0.1 Hz [3]. Such stimulation of the baroreflex is applied in the clinical practice for treating various diseases related to physical and mental disorders [4–7], as well as for assessing the functioning of the baroreflectory mechanism [8] and the physical and mental status of patients [9].

There are other hypotheses explaining the origin of ABP oscillations in the human CVS. For instance, the pacemaker theory [10, 1], which considers that central low-frequency rhythms formed in the brain stem can affect the heart rate and the peripheral vascular resistance via the sympathetic nervous system, resulting in low-frequency oscillations of the ABP. Moreover, ambiguity in understanding the nature of low-frequency oscillations in the CVS [1] allows one to revitalize old hypotheses, like the central volume one [11]. The idea of this hypothesis consists in the key role of the central blood volume, including the integral blood volume in the heart, lungs and central arteries, in the origin of low-frequency oscillations. Hence, the urgency of studying low-frequency oscillations in the human CVS is obvious from both practical (medical) and fundamental (biological) points of view.

Participation of autonomous control by the autonomic nervous system (ANS) in the forming of low-frequency arterial blood pressure oscillations is a well-established fact.

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However, the role of the hydrodynamic features of the cardiovascular bed (CVB) in this process still remains unclear. We assume that the CVB can respond to internal or external periodic stimuli by a gain in the amplitude of blood flow oscillations at frequencies close to 0.1 Hz, by itself, without the involvement of autonomous control.

To verify hypothesis suggested, we used mathematical modeling which is extensively applied in studying the mechanisms of blood flow regulation in the human CVS. Several approaches for modeling 0.1 Hz oscillations are used to study the mechanisms of autonomous regulation: modeling low-frequency excitation signals of the brain stem and the mechanism of the baroreflex feedback loop with a nonlinear element [12]; modeling short-term processes of autonomous regulation of the CVS and low-frequency fluctuations of peripheral resistance [13]; a model study of nonlinear effects including multifractal behavior [14]; studying the contribution of low-frequency component of the respiratory rhythm [15].

In the present study using a reduced hydrodynamic model of the systemic circulation we shown the conceptual possibility of an increase of blood flow oscillations at frequencies around 0.1 Hz, independently from the autonomous control when the oscillations are formed by low-intensity perturbations of the functioning of a single-chamber pump, which simulates the left ventricle of the heart.

MATERIALS AND METHODS

Blood flow oscillations were studied using a reduced hydrodynamic model of the systemic circulation [16]. The model of vascular bed consisted of the following elements: single-chamber pump (left ventricle of the heart) with the inlet and outlet valves, artery, peripheral artery, peripheral vein and vein (Fig. 1).

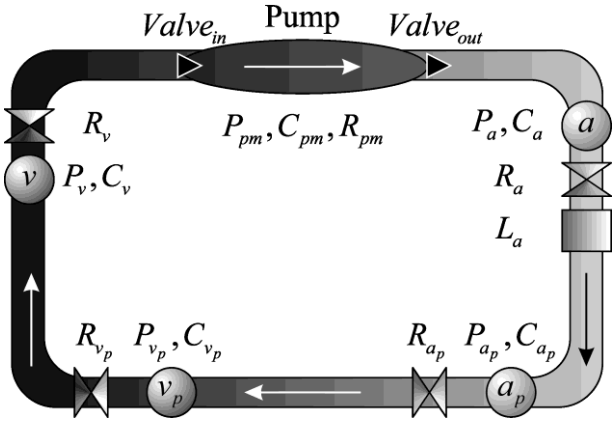

Fig. 1. Conventional scheme of the vasculature. Legend: P_i – blood pressure in vessel reservoir *i*; C_i and R_i – compliance and efficient hydrodynamic resistance of *i*-vessel reservoir correspondingly; pm – single-chamber pump a – artery; a_p – peripheral artery; v – vein; v_p – peripheral vein; L_a – inertia coefficient of the arterial blood flow. Pump – single-chamber two-valve pump ($Valve_{in}$ – inlet valve, $Valve_{out}$ – outlet valve). Arrows indicate blood flow direction.

The suggested model represents a system of equations, which describe the flow of viscous fluid through elastic reservoirs, the so-called Windkessel model [17]. The equations enable to calculate a number of parameters in vascular reservoir *i*: blood pressure (P_i), blood volume (V_i) and volumetric blood flow coming out of vascular reservoir *i* (Q_i) using such hydrodynamic parameters as compliance (C_i) and efficient hydrodynamic resistance (R_i) at the outlet of vascular reservoir *i*.

Single-chamber pump:

$$P_{pm}(t)=\frac{1}{C_{pm}(t)}\left(V_{pm}(t)-V_{u,pm}\right),$$
$$V_{pm}(t)=V_{total}-\sum_i V_i(t),\ i=a,a_p,v_p,v,$$
$$C_{pm}(t)=\frac{C_{pm\_\max}}{1+\frac{1}{2}(A-1)\left(1+\sin\left(2\pi f\cdot t\right)\right)}, \qquad (1)$$

where $V_{u,i}$ – unstressed volume of vascular reservoir i (here in after), $C_{pm\_\max}$ – maximal compliance of the pump in the diastolic (relaxation) phase, A – number of times, by which the maximal compliance is reduced in the systolic (contraction) phase, f – heart rate (HR) (rate of pump operation). Subscripts pm, a, a_p, v_p, v denote the pump, artery, peripheral artery, peripheral vein and vein, correspondingly. The value $E_{pm}(t)=1/C_{pm}(t)$ describes the rigidity of single-chamber pump walls changed over time.

Artery:

$$P_a(t)=\frac{1}{C_a}\left(V_a(t)-V_{u,a}\right),\qquad \frac{dV_a(t)}{dt}=Q_{pm}(t)-Q_a(t),$$
$$Q_{pm}(t)=\begin{cases}\dfrac{P_{pm}(t)-P_a(t)}{R_{pm}}, & P_{pm}>P_a,\\ 0, & \text{otherwise,}\end{cases}, \qquad (2)$$
$$\frac{dQ_a(t)}{dt}=\frac{1}{L_a}\left(P_a-P_{a_p}-R_aQ_a\right),$$

where L_a – inertia coefficient of the arterial blood flow. The equation (2) considers the functioning of the outlet valve, which opens when the pressure inside the pump exceeds the pressure in the arterial reservoir; otherwise, the valve is closed with the outlet flow being at zero level. From this point on we assume that the transition of the valves from the opened to the closed state happens instantly.

Peripheral artery:

$$P_{a_p}(t)=\frac{1}{C_{a_p}}\left(V_{a_p}(t)-V_{u,a_p}\right),\qquad \frac{dV_{a_p}(t)}{dt}=Q_a-\frac{P_{a_p}-P_{v_p}}{R_{a_p}}.$$

Peripheral vein:

$$P_{v_p}(t)=\frac{1}{C_{v_p}}\left(V_{v_p}(t)-V_{u,v_p}\right),\qquad \frac{dV_{v_p}(t)}{dt}=\frac{P_{a_p}-P_{v_p}}{R_{a_p}}-\frac{P_{v_p}-P_v}{R_{v_p}}.$$

Vein:

$$P_v(t)=\frac{1}{C_v}\left(V_v-V_{u,v}\right),\ \frac{dV_v(t)}{dt}=\begin{cases}\dfrac{P_{v_p}-P_v}{R_{v_p}}-\dfrac{P_v-P_{pm}}{R_v}, & P_v>P_{pm},\\ \dfrac{P_{v_p}-P_v}{R_{v_p}}, & \text{otherwise.}\end{cases} \qquad (3)$$

The equation (3) takes into consideration the work of the inlet valve, which opens if the pressure in the pump is lower than that in the venous reservoir, alternatively the valve is closed and the inward flow is equal to zero.

Table 1. Model parameters

Parameter	Value	Units
Pump		
$C_{pm\_\max}$	200	ml mmHg^{-1}
A	300	
$V_{u,pm}$	50	ml
V_{total}	4400	ml
R_{pm}	0.02	mmHg s ml^{-1}
Artery		
C_a	0.75	ml mmHg^{-1}
$V_{u,a}$	35	ml
R_a	0.18	mmHg s ml^{-1}
L_a	2.2×10^{-4}	mmHg s^2 ml^{-1}
Peripheral artery		
C_{a_p}	1.2	ml mmHg^{-1}
V_{u,a_p}	50	ml
R_{a_p}	0.92	mmHg s ml^{-1}
Peripheral vein		
C_{v_p}	210	ml mmHg^{-1}
V_{u,v_p}	274.4	ml
R_{v_p}	0.002	mmHg s ml^{-1}
Vein		
C_v	85	ml mmHg^{-1}
$V_{u,v}$	50	ml
R_v	1×10^{-3}	mmHg s ml^{-1}

The model parameters (Table 1) were selected so that the mean, systolic and diastolic pressure values in different reservoirs of the model CVB corresponded to normal physiological values under contraction frequency of the single-chamber pump $f = 1.2$ Hz (≈ 70 BPM), which is the normal physiological HR in human at rest (Table 2, Fig. 2).

Table 2. Mean values of blood pressure in the vessels. Experimental physiological data were taken from [19]

Vessel	Pressure (mmHg)	
	Physiological norm	Model
Aorta	100–120	99
Main arteries	100–120	
Branching arteries	80–90	86
Terminal arteries	80–90	
Arterioles	40–60	16
Capillaries	15–25	
Venules	12–18	
Terminal veins	10–12	
Branching veins	5–8	
Venous collectors	3–5	3
Hollow veins	1–3	

Computational analysis was carried out using module Simulink from Matlab R2014b software package using the Dormand–Prince algorithm for numerical calculation of ordinary differential equations with variable step integration. The resulting time dependencies were obtained for pressure in various vascular reservoirs (Fig. 2). Only dependencies for artery and peripheral artery were subsequently picked for spectral content analysis by adaptive wavelet transform [18].

In numerical experiments the basic frequency of the pump (f) was set to 1.2 Hz (≈ 70 BPM), which corresponds to normal heart rate in human at rest.

To determine the response of the model hydrodynamic system on periodic perturbations, the rigidity of chamber walls of the single-chamber pump were assumed to be perturbed by an additive periodic signal, additionally to the basic signal forming the contractile work of the pump. Thus the equation (1) was modified as follows:

$$C_{pm}(t) = \frac{C_{pm\_\max}}{1+\frac{1}{2}(A-1)\left(1+\left[\sin(2\pi f \cdot t)+\alpha\sin(2\pi f_m \cdot t)\right]/\left[1+\alpha\right]\right)}, \qquad (4)$$

where α – amplitude of the perturbing signal, which constituted 0.5% of the amplitude of the basic compliance oscillation of single-chamber pump walls, f_m – frequency of the perturbing signal which had values of 0.01, 0.033, 0.05, 0.08, 0.1, 0.15, 0.2, 0.33, 0.7, 1.2, 2 Hz. As seen from equation (4), perturbation provides normed changes of the compliance of single-chamber pump walls. That is to say that the maximal compliance change during contraction events in the perturbed system equals to the maximal compliance change in the unperturbed system.

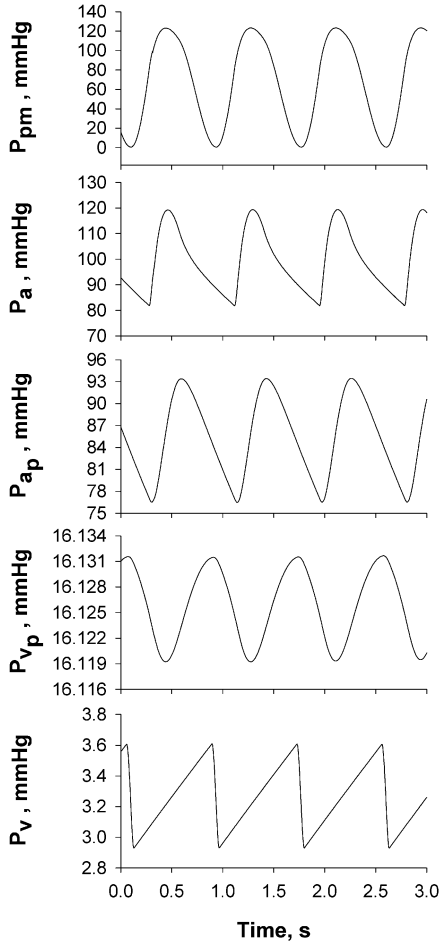

Fig. 2. Time dependence of blood flow in the model CVB for the following reservoirs: single-chamber pump (P_{pm}), artery (P_a), peripheral artery (P_{a_p}), peripheral vein (P_{v_p}) and vein (P_v).

Maximal values of spectral components corresponding to different frequencies of the perturbing signal were determined in the amplitude-frequency spectra of pressure in artery and peripheral artery for analysis of the CVS response on the periodic perturbation of compliance of single-chamber pump walls, and spectral envelopes were plotted.

The influence of hydrodynamic parameters of the CVB on the blood flow in the perturbed model system was evaluated through alteration of either compliance or resistivity of all vascular reservoirs simultaneously, excepting the single-chamber pump. To this end, we used the following values of coefficients of compliance K_C and resistivity K_R: $K_C = 0.33, 1, 3$, $K_R = 0.33, 1, 3$. The change of compliance or resistivity of vascular reservoirs derived from multiplication of their parameters by a corresponding coefficient.

RESULTS

Earlier studies of the CVB hydrodynamic model shown that oscillations of pressure and volumetric blood flow in the artery have a maximal amplitude at 0.1 Hz upon alteration of basic contraction frequency of the single-chamber pump in a wide frequency range (0.2–2 Hz) [20]. Thereof, if the basic frequency of the pump corresponds to normal human physiological values at rest, and the rigidity of single-chamber pump wall is subjected to additional perturbation by a periodic low-frequency signal, the appearance of an additional low-frequency component in the amplitude-frequency spectrum of arterial pressure can be expected, with a maximum value at a frequency close to 0.1 Hz.

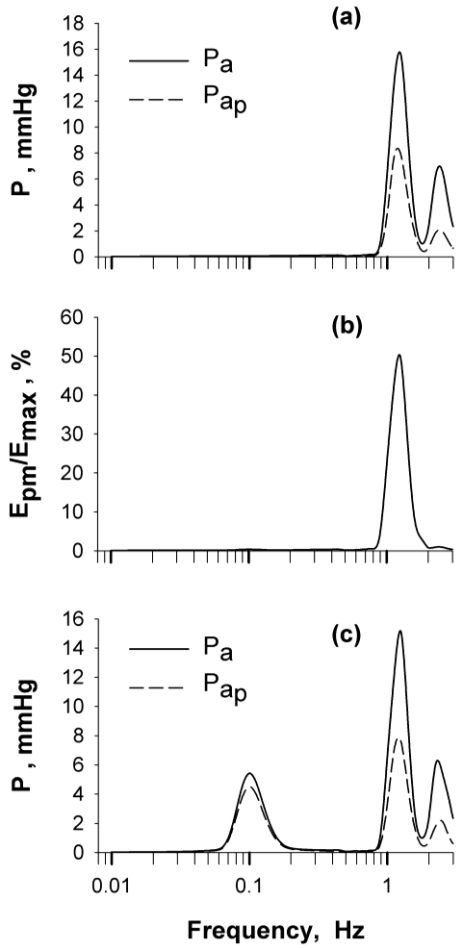

Fig. 3. Amplitude-frequency spectra: (a) pressure in artery (P_a) and peripheral artery (P_{a_p}) of the model CVB of unperturbed system; (b) specific rigidity of single-chamber pump walls in perturbed system; (c) pressure in artery (P_a) and peripheral artery (P_{a_p}) of perturbed system. Perturbation signal frequency was 0.1 Hz, with the amplitude of 0.5% of the basic oscillation.

First we evaluated the response of the model CVS on the periodic perturbation affecting the compliance of the single-chamber pump walls. The effect of periodic perturbation on the system was simulated according to equation (4). As seen in Figure 3, the spectra of blood pressure oscillations in the artery and peripheral artery in the absence of perturbation are composed of harmonic, which corresponds to the basic contraction frequency of the single-chamber pump, and additional high-frequency harmonics (Fig. 3,a). Figure 3,b demonstrates the oscillation spectrum of specific (normalized by the maximum value) rigidity $\tilde{E}_{pm}(t) = E_{pm}(t) / E_{pm,\max}$ of single-chamber pump walls upon affecting the model system with perturbation at a frequency of 0.1 Hz with an amplitude of 0.5% of the basic oscillation. It was shown that at 0.1 Hz the peak corresponding to perturbing oscillation $\tilde{E}_{pm}$ is scarcely noticeable against the basic oscillation peak at 1.2 Hz (Fig. 3,b). However, the system response to such perturbation, characterized by an alteration of pressure oscillations in artery P_a and peripheral artery P_{a_p}, contains a spectral component comparable in amplitude to the component of basic oscillation (Fig. 3,c). We discovered that in the analyzed model CVS small periodic perturbation of compliance of single-chamber pump walls in a low-frequency range results in significant alteration of pressure oscillations in the arterial part of the CVB.

The obtained result imposed the necessity of investigating the frequency localization. We estimated the response of the model CVS on the periodic perturbation of single-chamber pump wall compliance within a frequency range 0.01–2 Hz. The amplitude of the perturbing signal remained constant, being at 0.5% of the oscillation amplitude at the basic frequency 1.2 Hz.

Figure 4 shows the spectral envelope of pressure oscillations for the artery (P_a) and peripheral artery (P_{a_p}) at various frequencies of the periodic perturbation of single-chamber pump wall compliance. It is apparent that the spectral envelope of the low-frequency spectral components is bell-shaped, with a peak at 0.08 Hz, which is close to the frequency of 0.1 Hz.

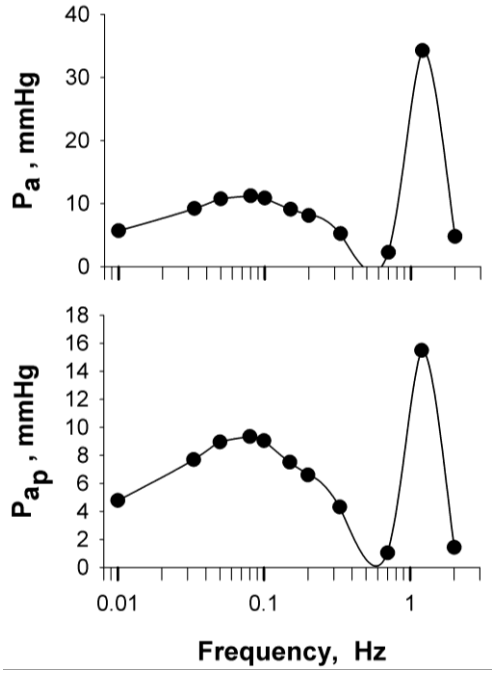

Fig. 4. Envelope of amplitude-frequency pressure spectra in artery (P_a) and peripheral artery (P_{a_p}) of the model CVB of perturbed system for various frequency values of perturbing signal. Perturbation signal amplitude was 0.5% of the basic oscillation.

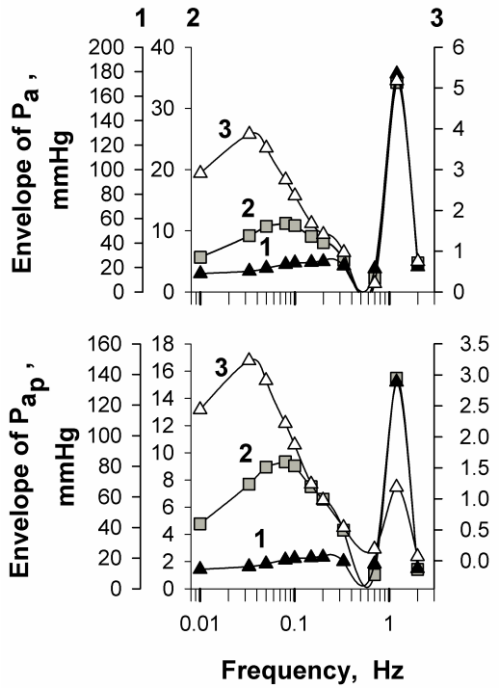

Fig. 5. Envelopes of amplitude-frequency pressure spectra in artery (P_a) and peripheral artery (P_{a_p}) of the model CVB of perturbed system for various frequency values of perturbing signal and various compliance coefficients: 1) $K_C = 0.33$, 2) $K_C = 1$, 3) $K_C = 3$. Perturbation signal amplitude was 0.5% of the basic oscillation.

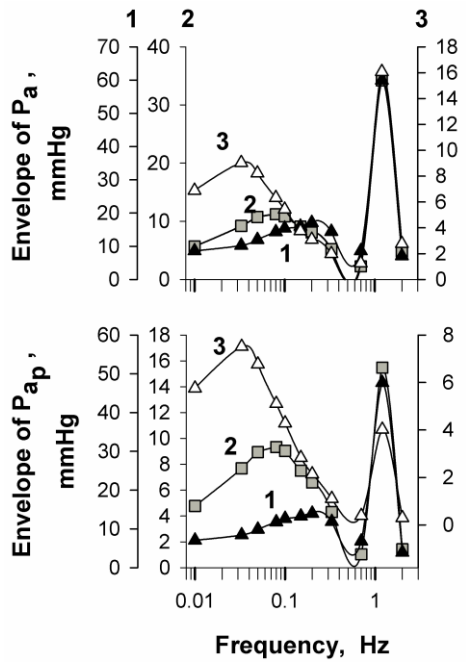

Fig. 6. Envelopes of amplitude-frequency pressure spectra in artery (P_a) and peripheral artery (P_{a_p}) of the model CVB of perturbed system for various frequency values of perturbing signal and various resistivity coefficients: 1) $K_R = 0.33$, 2) $K_R = 1$, 3) $K_R = 3$. Perturbation signal amplitude was 0.5% of the basic oscillation.

The hydrodynamic properties of distributed hydraulic system are largely determined by both the compliant characteristics of the pump, tube and reservoir walls, and the viscoelastic properties of the pumped liquid. For evaluation of the hydrodynamic properties of the model CVB we investigated the response of blood flow pressure in the arterial part of the CVB on the effect of the perturbing signal over a wide range of frequencies (from 0.01 to 2 Hz), with a

simultaneous change of compliance and resistivity parameters of all vascular reservoirs of the CVB excepting the single-chamber pump. Two cases were considered. The first one assumed a change of the compliance parameters under constant resistivity. In the second one, contrariwise, resistivity was alterable, while compliance was a constant. Spectral envelopes for the both cases are presented in Figure 5 and Figure 6. Obviously, alteration of compliance or resistivity of all vascular reservoirs results in a shifted position of peaks of the spectral component envelope on the frequency axis. The reduction of both compliance ($K_C = 0.33$) and resistivity ($K_R = 0.33$) of the vascular reservoirs leads to a shift of peak positions to a high-frequency domain up to 0.2 Hz, while the increase of these parameters ($K_C = 3$ and $K_R = 3$) shifts they towards the low-frequency range to 0.033 Hz.

Alteration of the hydrodynamic properties of vascular reservoirs of the model CVB causes the changes in the position of the spectral component envelope peak and in its amplitude. The magnitude of the peak is significantly reduced upon compliance increase and, to a lesser extent, the peak magnitude is decreased in the context of raised resistivity of vascular reservoirs (Fig. 7).

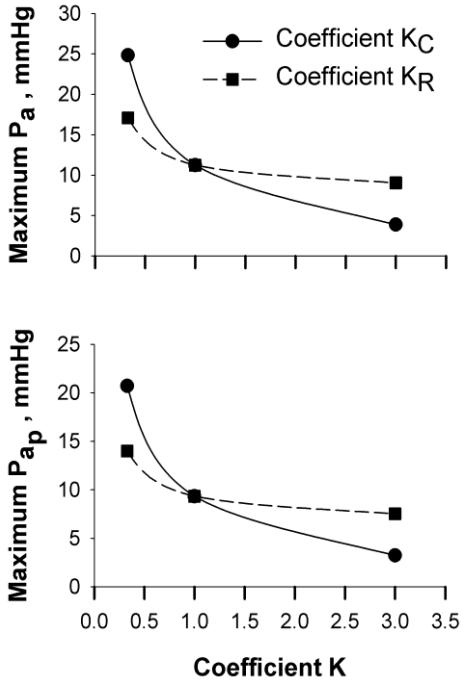

Fig. 7. Maxima envelopes for low-frequency components of amplitude-frequency pressure spectra in artery (P_a) and peripheral artery (P_{a_p}) of the model CVB of perturbed system for various coefficients of compliance (K_C) and resistivity (K_R).

DISCUSSION

We developed a simplified mathematical model of the human cardiovascular system for investigation of nonstationary hydrodynamic patterns of blood motion in the vasculature. Only the systemic circulation was taken into consideration, which includes up to 90% of the total volume of blood circulating in the cardiovascular system. It is known that blood motion through the systemic circulatory is realized by means of the pumping function of the left atrium and left ventricle. Since at rest the contraction of the left atrium contributes to diastolic blood filling of the left ventricle for less than 10%, it was excluded from analysis, and the functioning of the left part of the heart was simulated by a single-chamber pump simulating the left ventricle. The single-chamber pump in the model is represented by an elastic reservoir with a variable rigidity of chamber walls and two valves: inlet, letting the blood passes from the venous reservoir into the pump chamber, and an outlet, which releases the blood from the

pump chamber into the arterial reservoir. Model included certain reductions. First, the transition of the valve from the opened to the closed state happens instantly, instead of a physiologic time interval taking approximately 10% of time required for ventricular emptying. Second, the model does not consider vessel branching, and all vessels are divided into four classes corresponding to four generalized vascular reservoirs: arteries, peripheral arteries, peripheral veins and veins. Such reduced consideration of the heart and vasculature allows us to decrease the number of equations and model parameters, as compared to describing the four-chambered heart and branched vasculature. For the same reason we did not make allowance for blood heterogeneity, regarding it as a Newtonian fluid. Crucially, no links for ANS-mediated regulation of the blood flow in the cardiovascular system were included into the elaborated mathematical model.

The proposed mathematical model provides a simplified description of the human cardiovascular system, though considering the basic hydrodynamic properties of the CVB, which allows bringing into focus the search for hydrodynamic patterns associated with the oscillatory mode of blood motion in the vasculature.

The parameters of the mathematical model of the human cardiovascular system were picked so that the mean, systolic and diastolic pressure values in different reservoirs of the model CVB corresponded to normal physiological values under contraction frequency of the single-chamber pump $f = 1.2$ Hz (≈ 70 BPM), which is the normal physiological HR in human at rest. Such approach enabled us to link the hydrodynamic characteristics of the model with the physiological characteristics of the real cardiovascular system, allowing predicting the behavior of the CVS in different modes of functioning. It was found that upon perturbation of the cardiac pump wall rigidity by a periodic low-amplitude signal at frequencies lower than the basic frequency of pump contraction (1.2 Hz), additional spectral components are formed at frequencies of the perturbing signal in pressure oscillation spectra of the artery and peripheral artery, along with the spectral component corresponding to the basic frequency. They are comparable in amplitude with the basic frequency component, and the envelope of spectral components in the frequency range lower than the frequency of the basic oscillation is bell-shaped, with a peak at frequency close to 0.1 Hz, which is a characteristic frequency of Mayer waves in human. It was shown that the amplitude of response and the position of its maximal value on the frequency axis depend from such hydrodynamic parameters as compliance and resistivity of vascular reservoirs. A three-fold reduction of compliance or resistivity coefficients of vascular reservoirs leads to a shift of the envelope peak towards high frequency values and a raise of its amplitude, whereas a three-fold increase of these coefficients, conversely, provides a shift to the low-frequency range and amplitude reduction.

Using the developed model of the human cardiovascular system we demonstrated a fundamental possibility of an amplitude increase of low-frequency oscillations of the blood flow at frequencies close to 0.1 Hz, which has hydrodynamic nature and is not associated with the autonomous control by the cardiovascular system.

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