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METHODS

A Method for Assessing Stability of Regional Blood Circulation in Humans

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A new non-invasive method for assessing stability of functioning of the human regional circulatory system was developed. The method includes synchronous measurements of the level of cutaneous blood microcirculation of symmetrical areas of paired human organs by laser Doppler flowmetry and subsequent mathematical analysis of Dopplerograms using an original computational and experimental technique based on a mathematical model developed by us in the form of a system of differential equations describing experimental patterns of left—right asymmetry of oscillatory processes in the human regional circulatory system. The proposed method allows evaluating the reserve capabilities of the regional circulatory system in a patient and increases informative value of studies. This non-invasive method can be used in clinical practice to perform a personalized assessment of the stability of regional blood circulation and predict the risks of vascular pathologies.

Key Words: *stability; mathematical model; microcirculation; asymmetry; laser Doppler flowmetry*

Despite the improvement of functional diagnostic methods and significant scientific and technological progress in modern medicine, mortality from cardiovascular diseases remains high. WHO experts predict its further growth in both developed and developing countries, due to the aging of the population and lifestyle features [1]. Therefore, the developing quantitative methods for assessing the stability of blood circulation allowing prediction of the risks of vascular pathologies, is a pressing problem.

Strict mathematical definitions of the concept of stability and algorithms for its evaluation originate from the mathematical theory of stability of mechanical systems developed by Russian mathematician A. M. Lyapunov at the end of the XIX century [2]. This theory is widely used in the calculations of the stability of physical, mechanical, technical, and other systems. The main condition for the applicability of mathematical methods for assessing stability to any system is the availability of an adequate mathematical model of this system formulated in the form of a system of differential equations. Therefore, in order to develop accurate methods for assessing the stability of blood circulation, it is necessary to have an adequate mathematical model of the system under study. Currently, attempts are being made to construct mathematical models describing oscillatory processes in the human regional blood circulation system [3-5]; however, their formulation does not take into account the patterns of left—right asymmetry discovered by various researchers in the regulation of regional human and animal blood circulation [6-10]. It has been established that correlation relationships between microcirculation (MCR)

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parameters in symmetrical regions of paired organs play an important role in the mechanisms of regulation of oscillatory perfusion processes in different organs and tissues of mammals [6-8]. It was shown [9,10] that changes in the amplitudes of fluctuations in the microcirculation of symmetrical regions of paired organs depend on the initial values of these indicators not only of the same name, but also of the opposite side of observation. This indicates the systemic nature of the processes of regulation of blood flow in the symmetrical areas of paired mammalian organs and general patterns that are true for both microcirculatory and regional blood flow.

In previous studies [11], we formulated a mathematical model for the regulation of the parameters of MCR (PM_{left} and PM_{right}) of symmetrical areas of the upper extremities of a person with asymmetric physical exertion on them. However, this model is applicable only to one type of external influences: asymmetric loads on the upper limbs.

The purpose of this study was to develop methods for assessing the stability of regional blood circulation in humans based on a mathematical model not depending on the type of external influences and regions of observation.

MATERIALS AND METHODS

The method includes synchronous measurements for 2 min, with an interval of counts 0.05 sec, the level of cutaneous MCR of symmetrical authorities of paired human organs using a 2-channel analyzer LAKK-02 (LAZMA). On the basis of the obtained dopplerograms, a mathematical assessment of the stability indicators of the functioning of the MCR system of the studied regions was carried out. A multiple regression analysis of the relationships between the perfusion changes of each of the observation sides and the initial perfusion values of both the eponymous and the opposite side of the observation was performed. The parameters a0, a1, a2, b0, b1, b2 of regression equations were calculated:

$$\Delta x1 = a0 + a1x1 + a2x2 \quad \textbf{(1)},$$

$$\Delta x2 = b0 + b1x1 + b2x2 \quad \textbf{(2)}.$$

Here $\{x1[i]=PM_{left}[i]\}$ and $\{x2[i]=PM_{right}[i]\}$ are the current perfusion values of the left and right sides of the measurement, and $\{\Delta x1[i]\}$ and $\{\Delta x2[i]\}$ are the current values of their changes. Measurements were carried out in conventional (perfusion) units (pf. units). The significance of the regression analysis results was assessed by standard statistical methods. For this purpose, standard errors for regression coefficients (sa0, sa1, sa2, sb0, sb1, sb2) were calculated and the reliability of regression equations was estimated using the Fisher *F* test.

RESULTS

Regression analysis. To test the method, we measured MCR indicators in 5 healthy volunteers (men aged 50-70 years). Laser Doppler flowmetry signal sensors were fixed on the outer surface of the symmetrical edges of the lower parts of the right and left shoulder at points located 3 cm above the left fold. The time series reflecting the dynamics of synchronous measurements of the MCR indicators on the left ($x1=PM_{left}$) and on the right ($x2=PM_{right}$) are presented (Fig. 1, *a*), as well as instantaneous changes in these indicators Δx1 and Δx2 (Fig. 1, *b*) in one subject. Fluctuations the MCR indicators on the left and on the right are different, mutually non-overlapping stochastic processes. Statistical analysis of these processes performed for all 5 subjects showed that the mean value of the PM value on the left (6.97±0.94 pf. units) is slightly higher than on the right (5.48±0.89 pf. units), but this difference is not significant. Significant differences between the mean values of changes in Δx1 and Δx2 of these indicators on the left and right were also not revealed.

The next stage of the research was the study of quantitative patterns of changes in MCR indicators on the left and right. For this purpose, multiple regression analysis was used: regression coefficients a0, a1, a2, b0, b1, b2 of equations **(1)** and **(2)** were estimated for all fragments of periodograms for each subject (Table 1). The calculated values of the values of regression coefficients a2 in all subjects significantly differed from 0 ($p<0.05$). This indicates that changes in the MCR indicator on the left ($\Delta x1=\Delta PM_{left}$) depend not only on the initial values of this indicator on the left ($x1=PM_{left}$), but also on the value of this indicator on the right ($x2=PM_{right}$). A similar pattern also occurs for the right side of the observation: the calculated values of the regression coefficients b1 in all subjects significantly differed from 0 ($p<0.05$). Thus, the changes in the MCR indicators on the right ($\Delta x2=\Delta PM_{right}$) depend not only on the initial values of this indicator on the right ($x2=PM_{right}$), but also on the value of this indicator on the left ($x1=PM_{left}$).The results of the regression analysis indicate that the changes in the amplitudes of fluctuations in the microcirculation of symmetrical areas of the upper extremities depend on the initial values of these indicators not only of the same name, but also of the opposite side of the observation.

Examples of the initial and calculated, according to regression equations **(1)** and **(2)**, time series describing the instantaneous values of changes in Δx1 and Δx2 of MCR indicators for one of the subjects are shown in Figure 2. The calculated curves of changes in Δx1 and Δx2 describe the initial curves of changes in MCR indicators quite well. Further verification using

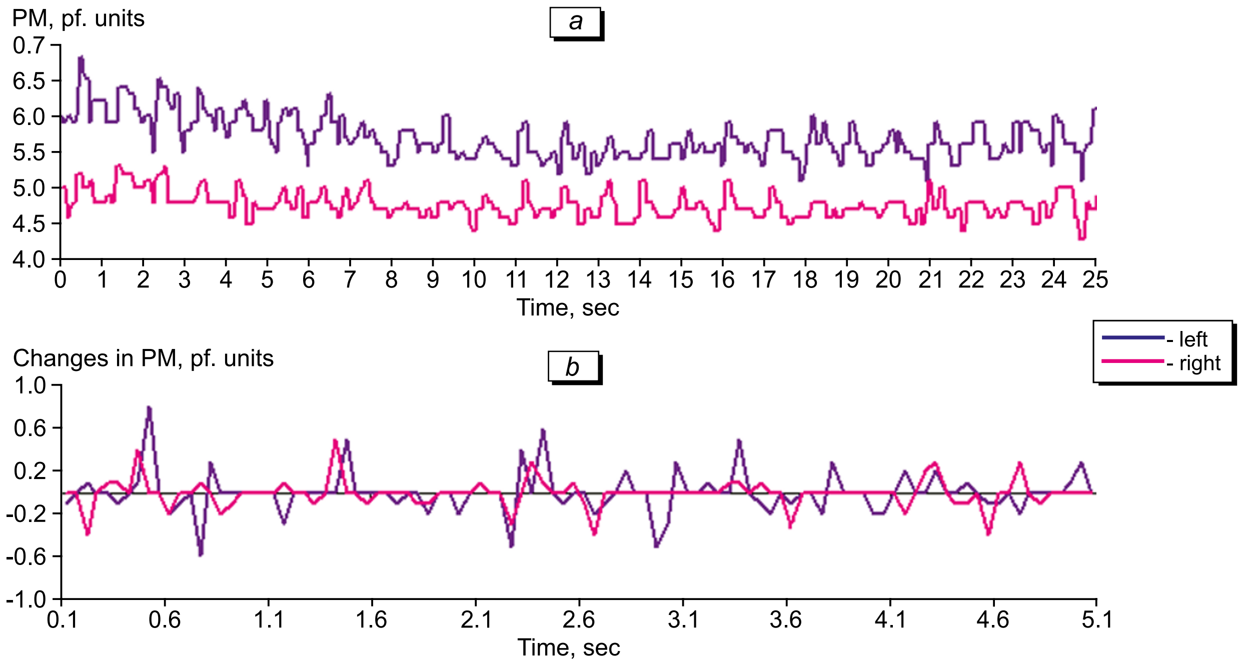

Fig. 1. Dynamics of changes in MCR parameters on the left ($x1=PM_{left}$) and on the right ($x2=PM_{right}$) (*a*), as well as their changes Δx1 and Δx2 in one subject (*b*).

Fischer's *F* criterion showed the statistical reliability of the chosen regression model in all 5 subjects. Thus, the computational and experimental technique used made it possible to formulate a statistically significant regression model describing the dynamics of synchronous changes in the MCR indicators of symmetrical areas of the upper extremities of a person.

Mathematical model. The regularities of changes in the MCR indicators described by the system of regression equations **(1, 2)** give reason to believe that with small changes $\{\Delta x1[i]\}$ and $\{\Delta x2[i]\}$ (and this really took place, since the interval of the periodogram $\Delta t[i]=0.05$ sec) the system of regression equations **(1)** and **(2)** can be replaced by a system of differential equations:

$$dx1/dt=a0+a1x1+a2x2 \quad \textbf{(3)},$$

$$dx2/dt=b0+b1x1+b2x2 \quad \textbf{(4)}.$$

Therefore, the mathematical model describing the experimental patterns of left—right asymmetry of oscillatory processes in the system of regional human circulation is based on a system of differential equations **(3)** and **(4)**.

Stability of regional blood circulation processes. One of the important questions that arise in the study of physiological systems is the question of the mechanisms for ensuring the stability of their functioning. The results of this study indicate that the functioning of the human regional circulatory system is subject to strict mathematical laws described by a system of linear differential equations **(3)** and **(4)**, therefore, the study of the stability conditions of this system can be performed by standard mathematical methods. According to the Hurwitz criterion, the study of the stability of a system of linear differential equations of the *n*-th order

TABLE 1. Calculated Values of the Mean Values of the Regression Coefficients for All 5 Subjects (*M*±*m*)

Regression coefficient, arb. units	Subject No.				
	1	2	3	4	5
a2	0.143±0.064*	0.187±0.043*	0.139±0.053*	0.135±0.051*	0.184±0.037*
a1	-0.294±0.021	-0.366±0.027	-0.317±0.048	-0.426±0.032	-0.282±0.018
a0	1.024±0.289	1.313±0.222	1.651±0.225	1.940±0.342	0.534±0.219
b2	-0.363±0.023	-0.318±0.027	-0.303±0.063	-0.284±0.031	-0.307±0.025
b1	0.132±0.031**	0.104±0.024**	0.135±0.044**	0.151±0.037**	0.078±0.021**
b0	0.990±0.110	1.421±0.182	0.305±0.059	1.305±0.215	0.859±0.193

Note. *a2>0, $p<0.05$; **b1>0, $p<0.05$.

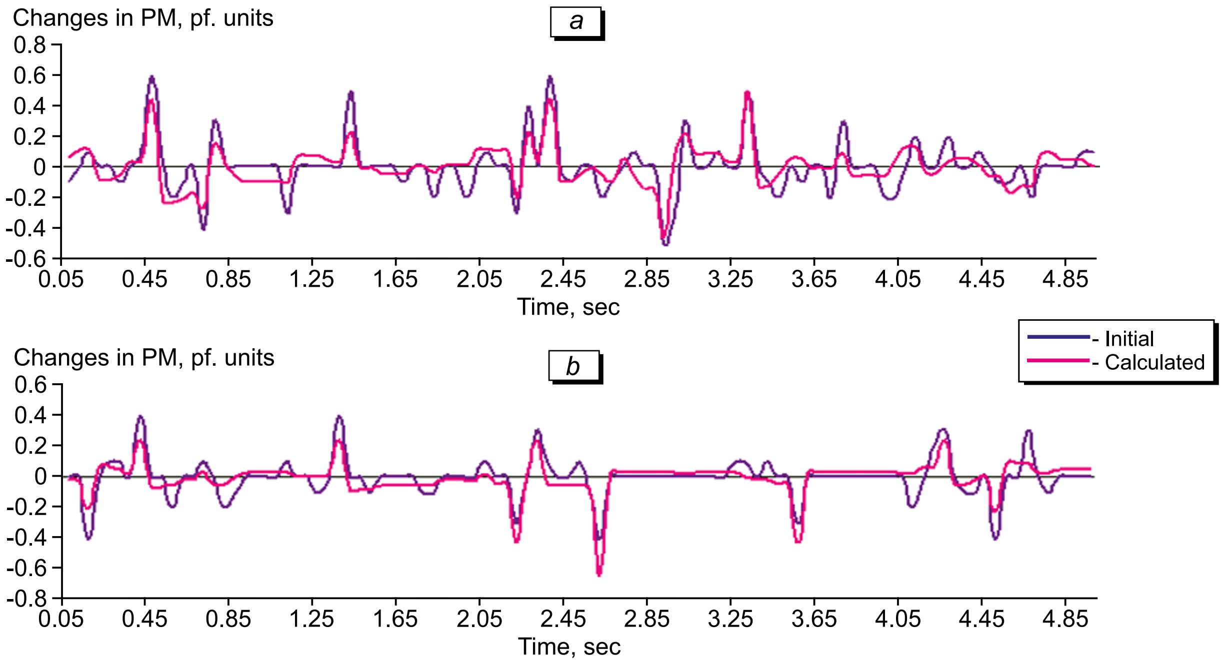

Fig. 2. Initial and calculated time series describing the instantaneous values in Δx1 (*a*) and Δx2 (*b*) MCR parameters for one subject.

is reduced to finding the conditions for the negativity of the real parts of the corresponding characteristic equation. In our case, the system of differential equations **(3)** and **(4)** will have stable solutions if:

$$T1=1/(a1b2-b1a2)>0 \quad (5),$$

$$T2=-(b2+a1)/(a1b2-b1a2)>0 \quad (6).$$

Moreover, the values T1 and T2 are connected by the condition:

$$\zeta=T2/2T1<1 \quad (7).$$

This condition means that the roots of the corresponding characteristic equation are complex. Since the system of differential equations **(3)** and **(4)** describes an oscillatory process, the characteristics of which depend on the specific numerical values of the parameters a0, a1, a2, b0, b1, b2, then depending on the value of ζ, different behaviors of the oscillatory system under study are possible. With the growth of ζ, the oscillation of the transient process decreases, disappearing completely at ζ=1.

Thus, the proposed model allows us to assess the stability of blood circulation processes in the microcirculatory bed. During testing of all subjects for the stability of the MCR system, numerical values of the parameters T1, T2 and ζ were calculated and the conditions were checked **(5)**, **(6)**, **(7)**. The values of the regression coefficients in all subjects satisfied the stability conditions, unstable states were not detected (Table 2).

Stability markers T1, T2, ζ **(5-7)** allow for a personalized assessment of the stability of regional blood circulation of patients. For a visual representation of the degree of stability or instability of the regional circulation of the subject, a graphical representation of the localization of the calculated points on the coordinate planes a1(a2) and b1(b2), in which the boundaries of the stability zones are indicated (Fig. 3). If the localization of the experimental points a1(a2) and b1(b2) is located inside the stability zones of both

TABLE 2. Regression Coefficients (a1, a2, b1, b2), Parameters T1, T2, ζ, and the Results of Testing the Mathematical Model of Stability for All 5 Subjects

Subject No.	Regression coefficient				Stability condition					
	a1	a2	b1	b2	T1	T1>0	T2	T2>0	ζ	ζ<1
1	-0.294	0.143	0.132	-0.363	11.384	true	7.479	true	0.329	true
2	-0.366	0.187	0.104	-0.318	10.316	true	7.056	true	0.342	true
3	-0.317	0.139	0.135	-0.303	12.939	true	8.022	true	0.310	true
4	-0.426	0.135	0.151	-0.284	9.940	true	7.058	true	0.355	true
5	-0.282	0.184	0.078	-0.307	13.846	true	8.155	true	0.295	true

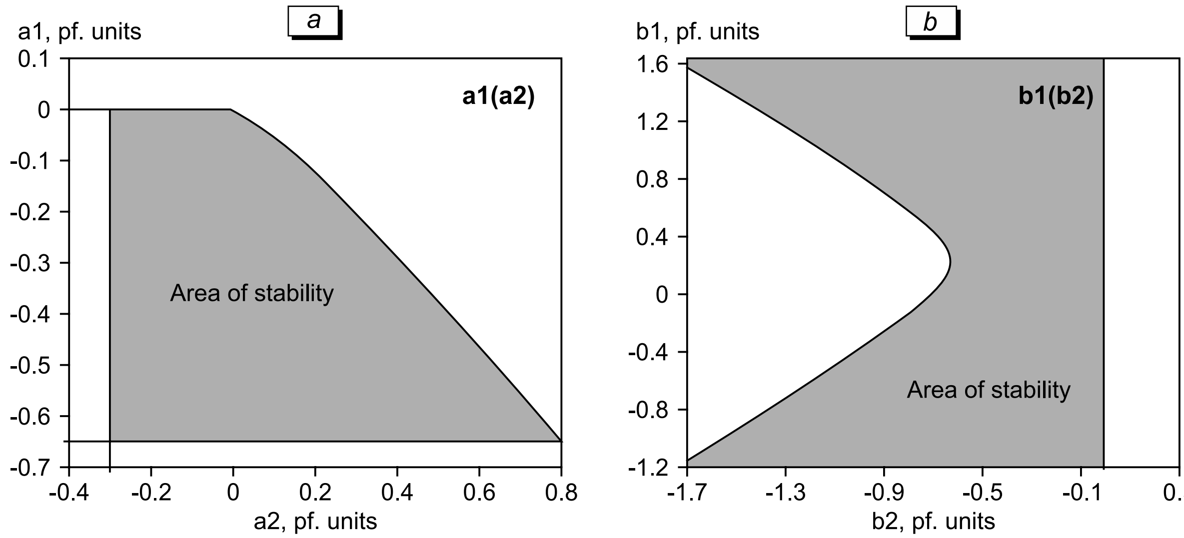

Fig. 3. Areas of stability of the parameters of the mathematical model. *a*) Plane of parameters (a2, a1); *b*) plane of parameters (b2, b1).

coordinate planes, the system is stable. All changes in the localization of experimental points that do not go beyond the boundaries of stability correspond to compensatory changes. The exit of experimental points beyond the boundaries of the stability zone indicates the presence of pathological changes. The further the experimental points go beyond the boundaries of the stability zones, the greater the risk of critical states.

The proposed method makes it possible to identify a preclinical tendency to diseases of the vascular system, assess the reserve and adaptive capabilities of the regional circulatory system, and predict the occurrence of pathological regimes and critical conditions.

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