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METHOD FOR EARLY DIAGNOSIS OF CORONARY HEART DISEASE: MODELING THE KINETICS OF AMINE METABOLISM AND THE DEVELOPMENT OF CARDIOSCLEROSIS

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Introduction: Currently, early diagnosis of coronary heart disease (CHD) remains the most pressing task in cardiology. The gas analytical method for analyzing exhaled air (EX) is a new approach to solving this problem [1]. Our theoretical and clinical studies, carried out with the aim of developing a non-invasive method for diagnosing IHD, led to the following main results: IHD is accompanied by a violation of the metabolism of biogenic amines [2], volatile amines are found in the composition of explosives in patients with IHD [3, 4], the most significantly increased diethylamine content in EVs in patients with post-infarction cardiosclerosis (PICS) [5], secondary amines (SAs) can be formed during the reduction of Schiff bases (SB) under conditions of acidosis in cellular sarcosomes of cardiac tissue [6].

However, the nature of the dependence of the kinetic parameters of VA formation on the degree and scale of ischemic zones of the myocardium remains unclear.

The aim of this work is to construct a semi-empirical model for studying the process of development of cardiosclerosis and to obtain the dependence of the kinetic constants of VA exchange rates on some geometric characteristics of ischemic zones on the myocardial surface.

MATERIAL AND METHODS

We previously [5] found a statistically significant difference in the content of volatile amines in explosives in patients with ischemic heart disease. PICS compared to healthy people. To study VA in the IV of patients with coronary artery disease during the treatment period, we used a gas analytical method. To obtain IV samples in a hospital setting, 16 men diagnosed with IHD were examined. PICS at the age of 39-64 years and for 10 days, IV tests were performed daily 4 times a day. The diagnosis in all patients was made based on clinical observation, laboratory analysis and functional diagnostics. For 3-15 years, patients underwent inpatient and outpatient treatment. Explosive samples were obtained using traps using double-distilled water as an absorber in a volume of 200 ml.

RESULTS

Based on a statistical analysis of the results of measurements of the VA content in explosives, the following values of gas analytical indicators were obtained: M_1 ; M_2 ; m_1 ; m2 . M_1 – average value of amine content in the first half of the observation period of patients (320 observations).

M_2 - the same, only in the second half of the observation period (320 observations).

m_1 and m_2 – dispersion of the gas analytical indicator in the first and second halves of the observation period of patients. Accordingly: M_1 =600; M_2 =250 m_1 =120; m_2 =80. These values are given in units of 10^{-9} g/l.

By Student's test t = 2.3.

The results obtained show that during the treatment of patients, the content of amines in the explosives decreases statistically significantly (t >2).

The statistically significant difference in the content of VA in EVs in patients with PICS, which we discovered in this work, shows that during the treatment the metabolism of biogenic amines changes significantly. Volatile components of biogenic amines can be formed during the reduction of Schiff

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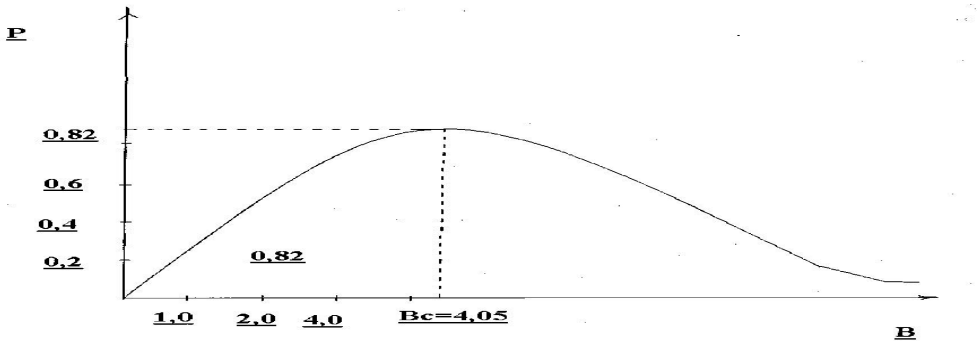
bases, which are the main products of lipid peroxidation (6). As is known, SHO can be formed by the interaction of aldehydes with primary amines. This mechanism, proposed by Mannich, is found in plants and is called the Mannich reaction. In the human body, under conditions of initiation of lipid peroxidation, a qualitative change in the activity of monoamine oxidase (MAO) occurs (7, 8). A decrease in the activity of MAO in relation to the deamination of primary amines, and vice versa, an increase in its activity towards diamines leads to the accumulation of primary amines and various aldehydes. Therefore, under LPO conditions, SHO accumulation occurs. Reduction of SH leads to the formation of volatile metabolites of biogenic amines in the form of secondary amines. Thus, we propose a new mechanism for the formation of secondary amines in the human body under LPO conditions. It was previously shown that SHOs can be restored during their interaction with adrenaline, and clinical observations of the content of volatile metabolites of biogenic amines in EVs in patients prove the possibility of such a mechanism. Therefore, activation of the sympatho-adrenal system should stimulate the process of restoration of the SB. This is exactly what happens in the initial stage of development of NQMI , which we also identified based on clinical studies. Since we treat IHD in combination with antioxidant therapy and standard therapy, we can conclude that suppression of LPO led to the restoration of metabolic disorders of biogenic amines. This is evidenced by the dynamics of the decrease in volatile metabolites of biogenic amines in EVs in PICS patients during treatment with antioxidants. To study the kinetics of VA formation at the interface between intact tissue and ischemic tissue, we propose a new model for studying the development of cardiosclerosis.

1. Model for studying the process of cardiosclerosis

To study the features of the development of cardiosclerosis, the following modeling algorithm based on the Monte Carlo method has been developed.

1. Selection of intact cardiac tissue surface with area S.
2. On the intact surface S, a random choice of the coordinate of the origin of a localized ischemic zone (LIZ) with an area S_0.
3. Determination of the number of LYS- ng appearing at the interface between intact and ischemic tissue.
4. Calculation p = ng / n , where n is the total number of LIZ.
5. Calculation $B = S_0 / S \times n$.
6. Construction of the dependence p= F (B).

Based on this algorithm, a program was compiled for the IBM PC in the algorithmic language Q - BASIC and the universal dependence p = F (B) was obtained (see Fig. 1)



Rice. 1. Origin of a localized ischemic zone depending on the degree of myocardial ischemia

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As can be seen from Figure 1, with increasing B, p increases and reaches a maximum. Number B characterizes the degree of ischemicity of myocardial tissue, p is the probability of the occurrence of lyses at the interface between ischemic and normal tissue. Thus, with the random generation of LYS on the surface of intact cardiac tissue, there is a critical value - $B = B c_{at}$ which LYS, overlapping, form the most developed interface between the intact and ischemic zones of the cardiac tissue. This universal dependence allows us to divide the process of development of cardiosclerosis into several stages.

1. B<Bc is a reversible stage of acute dystrophic changes.
2. B=Bc is the critical stage of transition from reversible changes to irreversible ones.
3. B>Irreversible stage of acute dystrophic changes.

Thus, a favorable outcome of treatment for IHD depends largely on the possibility of diagnosing it at the first stage, when B<Bc.

2. Kinetics of formation of secondary amines

In ischemic areas, the formation of SH occurs (6). Violation of microcirculation in these zones leads to a deterioration in their outflow from the ischemic zone and their further excretion from the body. Therefore, it can be assumed that CO accumulates at the border between normal and ischemic tissue. Their further restoration and outflow into the microcirculatory bed of intact tissue leads to the appearance of VA in the IV. To study the kinetics of these processes, consider the following system of kinetic equations.

$dn_1/dt=-k_1 n_1$

$dn_2/dt=k_1 n_1 – k_2 n_2$

$dn_3/dt = k_2 n_3$

n_1 – concentration of SH in LIZ

n_2 – concentration of VA in the blood

n_3 – concentration of VA in explosives

The time during which the maximum concentration of VA in the blood is established is determined by the following formula:

$t = \ln (k_1 / k_2) / (k_1 - k_2)$ (1)

where l_n is the sign of the natural logarithm, and to_1 is the rate constant for the reduction of SHO to VA. k_2 – rate constant for the removal of VA from the microcirculation of cardiac tissue.

The critical value of the degree of ischemia B_c can be expressed through V_c - the frequency of the onset of lyses using the following formula:

$B_c=S_0 Vc\, l_n(x)/ [Sk_2 (x-1)]$

Here $x = k_1 / k_2$ characterizes the ratio of inflow to outflow of VA in the microcirculation bed of cardiac tissue. As can be seen from this formula V_c increases with x. Therefore, for the development of MI, the LPO intensity must cross the boundary $V = V_c$. This limit depends on x and as x increases, the threshold value V_c increases. Based on the results of this theoretical analysis, X can be called the kinetic coefficient of resistance of a living organism to LPO factors.

THE DISCUSSION OF THE RESULTS:

Theoretical analysis shows that LIZs connecting with each other form larger islands of myocardial ischemia. There is a critical value of parameter B, at which a qualitative change occurs in the course of IHD, characterized by the transition of reversible dystrophic changes in the myocardium to irreversible ones. The interface between ischemic and normal tissue increases and is well described by parameter B.

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If the frequency of V generation is related to the intensity of LPO, then we obtain a relationship between VA and the geometry of the location of LYS on the myocardial surface. Clinical observation of amines in the composition of explosives in patients with coronary artery disease shows that this indicator is quite sensitive to the condition of patients with coronary artery disease. The relative change in not only the average value, but also the dispersion of the amine content in EVs indicates that the geometry of the interface between normal intact tissue and ischemic tissue plays a significant role in the mechanism of EV formation.

Thus, the amount of LYS increases with increasing LPO intensity and decreasing x, that is, decreasing by $_1$ or increasing by $_2$.

However, there is a critical value n that is constant for any variations of the parameters S , S_0, V , k_1 and k_2. therefore, at a critical degree of ischemia and at given values of S0 and S , an increase in V is also accompanied by an increase in x, i.e. to $_1$. Since k_1 depends on the process of restoration of the sho, it can be assumed that all processes that stimulate restoration processes contribute to the transition to the irreversible stage of acute dystrophic changes in the myocardium. This conclusion is consistent with the fact of the development of cardiosclerosis under conditions of activation of the sympathetic-adrenal system.

CONCLUSIONS

1. A model for studying cardiosclerosis has been constructed.
2. A universal parameter characterizing the degree of cardiosclerosis has been found.
3. Using a universal parameter, post-infarction cardiosclerosis was differentiated according to its geometric characteristics.
4. A connection has been established between the parameter characterizing the degree of myocardial ischemia and the kinetic constants of the formation of secondary amines.

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