Prognostic heterogeneity of diastolic abnormalities along left ventricular remodeling continuum according to survival rates and laser polarimetry of blood

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1. INTRODUCTION

Heart remodeling, including that of left ventricle (LV), is a self-sufficient pathophysiological process leading to the progress of heart failure (HF) irrespective of neurohumoral status [1]. The variety of LV remodeling patterns is explained by the complex hierarchy of structural and functional levels of its arrangement: from treating it as a "hydrodynamical system of input-output" on the level of the integral organism to genetically determined network of molecular interconnections (genomics, protheomics, lipidomics) in the cells and extracellular matrix. This approach is based on the multiplicity of pathophysiological factors participating in the remodeling process, including non-cardiomyocyte ones (the concept of "polycellular tissue pump") [2].

All these numerous factors due to modern paradigm of HF development and progress can act as the "syndrome modifiers" defining its individual course and prognosis: arterial hypertension (AH), degree of atherosclerosis process, endothelial dysfunction, metabolic disorder, etc. [3]

Nowadays the Seattle Heart Failure Model (SHFM) is one of the most available models for individual determination of HF prognosis. By way of considering a number of clinical, laboratory and instrumental parameters it enables to determine 1-, 2- and 5-year survival [4]. However, this model does not account the whole complexity of progressing process and heterogeneity of HF prognosis, especially in terms of the preserved ejection fraction (EF) of LV, i.e. it demands being further improved and supplemented with other sufficient prognostic parameters.

The disorder of functional properties of erythrocytes as the corpuscles of integrative environment – blood – can be regarded as a potential "modifier" of HF syndrome [5-23]. Modern literature does not contain enough data as to the erythrocytes functional properties positioning in the integral aspect as possible predictors of myocardium state and the prognosis as to its remodeling. This is partially related to methodological difficulties.

Biophysical approach to blood and its components as to optically inhomogeneous media with the use of corresponding research techniques represent one of the ways to study such interactions.

Optically the structure of any biological tissue, including blood, as a type of the connective one, is described by two-component amorphous-crystalline structure. The crystalline component of extracellular matrix is an architectonic network of coaxial cylindrical fibrillar protein molecules possessing the properties of uniaxial anisotropic birefringent crystals. Thus, biological tissue has optically isotropic and anisotropic components [6,7].

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Functional properties of erythrocytes are determined by a complex molecular arrangement that includes a great amount (about 900) and variety of protein structures including fibrillar ones [9]. These properties determine the ability of an erythrocyte to transform the parameters of laser radiation by the emergence of elliptically polarized laser waves and the possibility to analyze polarization heterogeneity of the images of smears of erythrocytic suspension by way of laser polarimetry [8, 14].

Taking into account all mentioned above, it can be assumed that the changes of polarimetric properties of erythrocytes on the stages of cardiovascular continuum represent potential additional, sufficient prognostic "modifier" of HF syndrome and studying them is important concerning the integrative approach to understanding the process of myocardium remodeling.

That is why the aim of this research is to study the interconnections of survival parameters, functional state of LV myocardium and optical properties of erythrocytes at various LV remodeling patterns of the patients suffering from AH and coronary heart disease (CHD).

2. OBJECT AND METHODS OF INVESTIGATION

35 male patients with AH (essential), CHD and various stages of HF took part in the analytical cross-sectional study. Verification of AH, its degree and stages, clinical forms of CHD (stable angina pectoris of II and III functional class (the Canadian Cardiovascular Society Classification), diffuse and postinfarction cardiosclerosis), HF functional class (NYHA) was performed according to up-to-date recommendations and standards [2, 5]. The average age of the patients was 60 (54-66), the average AH duration – 10 (3-21) years. The examined patients signed the informed consent forms of participation in the research.

All patients underwent complex examination, including anthropometrics (height, mass and body surface area (BSA) by Du Bois formula) [1] and paraclinical laboratory tests.

The echocardiographic examination was performed by means of ultrasound scanner Philips EnVisor (USA) using standard techniques with the analysis of heart cavities sizes (including the volume of left atrium (LAV), indexed by BSA (LAV_i, ml/m^2)); cardiohaemodynamics (EF of LV, %); calculation of LV myocardium mass (LVMM) with indexation by BSA (LVMM/BSA, g/m^2); performing pulse wave Dopplerography. The parameters of transmittal flow, particularly the speed of early diastolic filling (E, cm/s) and the parameters of mitral valve's fibrous annulus kinetics including early diastolic velocities of septal (e_{sept}, cm/s) and lateral (e_{lat}, cm/s) parts and their average values (e_{av}, cm/s) were investigated dopplerographically. The relation of E to e (E/e_{sept}, E/e_{lat} and E/e_{av}) were calculated respectively.

Verification of diastolic dysfunction (DD) of LV and elevation of LV end-diastolic filling pressure (EDFP) was performed according to guidelines [1, 11].

The investigated group of patients was stratified into 4 remodeling patterns of LV: pattern 1 (P_1) – sinus rhythm, diastolic function of LV is not abnormal (n = 8 (22,9%), pattern 2 (P_2) – sinus rhythm, DD of LV, EDFP of LV is not elevated (n = 11 (31,4%), pattern 3 (P_3) – sinus rhythm, DD of LV, EDFP of LV is elevated (n = 5 (14,3%) and pattern 4 (P_4) – patients with stable atrial fibrillation (AF), DD of LV, with elevated LV EDFP (n = 11 (31,4%).

The prognosis parameters (1-, 2- and 5-year survival (S_1, S_2, S_5), mortality rates (M_1, M_2, M_5); mean life expectancy (MLE)) were calculated according to Seattle Heart Failure Model (SHFM) basing on such predictors as: age, body mass, HF NYHA class, the value of systolic arterial pressure, CHD occurrence, the results of complete blood count (hemoglobin and lymphocytes levels), total cholesterol, uric acid and sodium of blood plasma, EF of LV [15].

This research did not include the patients with the signs of moderate and severe anemic syndrome and the III stage of HF.

The study of optical birefringence of washed erythrocytic suspension smears was performed in the conventional setup of laser polarimeter (Fig.1) [16].

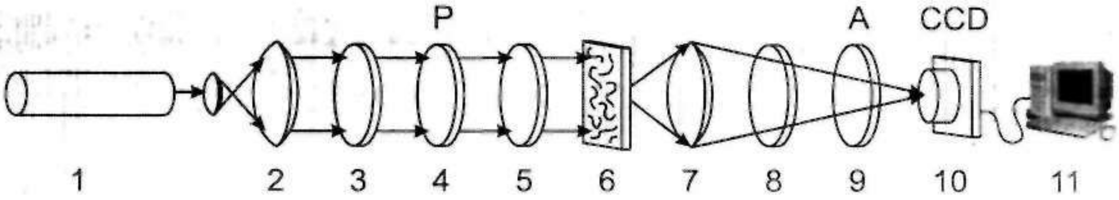

Fig.1 Optical scheme of polarimeter, where: 1 – He-Cd laser; 2 – collimator; 3, 5, 8 – quarterwave plates; 4, 9 – polarizer and analyzer respectively; 6 – object of investigation (erythrocytic suspension smear); 7 – microobjective; 10 – CCD camera; 11 – personal computer

Irradiation of erythrocytic suspension smears was performed by collimated beam ($\varnothing = 10^4$ μm) of He-Cd laser ($\lambda = 0{,}441$ μm). By means of polarization light source (quarterwave plates 3, 5 and polarizer 4) different polarization states of the illuminating beam were formed. Polarization images of erythrocytic suspension smear (6) were projected by microobjective 7 on the plane of light sensitive plate (800x600) of CCD camera (10).

By rotating the transmission axis of analyzer 9 by the angle Θ within 0° – 180° the arrays of minimal and maximal intensity levels $I_{min}(m \times n); I_{max}(m \times n)$ of erythrocytic suspension smears images were determined fort every particular pixel (mn) of CCD-camera. Then the values of polarization ellipticity (β) of erythrocytic suspension smears images were calculated using the following relation (1):

$$\beta(m \times n) = arctg \frac{I_{min}(m \times n)}{I_{max}(m \times n)}$$

(1)

For objective characteristics of the statistical structure of coordinate distributions β (polarization maps) of erythrocytic suspension smears laser images the ensemble of statistical moments of the 1st-4th order (Z_1 (median), Z_2 (dispersion), Z_3 (asymmetry) and Z_4 (excess) respectively) was used, calculated from relations (2):

$$Z_1 = \frac{1}{N}\sum_{i=1}^{N} |(\beta)_i|;$$
$$Z_2 = \sqrt{\frac{1}{N}\sum_{i=1}^{N} (\beta)_i^2};$$
$$Z_3 = \frac{1}{Z_2^3}\frac{1}{N}\sum_{i=1}^{N} (\beta)_i^3;$$
$$Z_4 = \frac{1}{Z_2^2}\frac{1}{N}\sum_{i=1}^{N} (\beta)_i^4, \quad (2)$$

where $N = 800 \times 600$ – total amount of pixels of CCD-camera 10 (Fig.) registering polarizationally heterogeneous field of erythrocytic suspension smears [6-8, 14].

The material was statistically analyzed using the software suites Statistica v. 8.0 (StatSoft Inc., USA) and Minitab v. 16.0 (SafeNet Inc., USA). The comparison of the absolute and relative frequencies of nominal and order parameters was performed using the tables of cross-tabulation with Pearson χ^2 criterion assessment, and in the case of its mathematical instability – the tables "2x2" and the significance assessment of the exact Fisher's test. The cluster analysis was carried out by K-means technique. To compare the quantitative parameters the non-parametric dispersion analysis was applied. The central tendency and variation of the parameters were designated as Me (Q_{25}-Q_{75}), where Me – median, Q_{25} and Q_{75} – upper and lower quartile correspondingly. Correlation (r) was determined by means of Spearman's correlation analysis. The regressive analysis was performed with the use of the logistic regression model and a goodness-of-fit Hosmer-Lemeshow test. The level of statistical significance for correlation coefficient was $p < 0.05$. For the comparison of quantitative parameters in independent samples the Bonferroni correction was used and statistical significance level amounted to $p < 0.008$. At the adequacy of logistic regression equation the frequency of concordant pairs predominated, as well as $p > 0.05$ for χ^2 criterion in the Hosmer-Lemeshow test.

3. INVESTIGATION RESULTS AND DISCUSSION

Table 1-3 presents the characteristics of the group of patients under examination. The patients of P_1 were characterized by the preserved systolic and diastolic functions, while those of P_2 – by asymptomatic DD of LV myocardium, i.e., they did not have HF in the classical sense. The patients of the above mentioned patterns, according to HF classification of the American Heart Association /American College Cardiology demonstrate a rather spread asymptomatic stage B with powerful predictors of HF development [10]. However, the survival parameters were also calculated for them, as a wide range of prognostic predictors is presupposed by SHFM, including EF of LV, also for the contrast of those with the patients being at the more remote stages of cardiovascular continuum (P_3 and P_4).

Table 1

Clinical and echo-characteristics of patients at different left ventricular remodeling patterns

	P_1 n = 8	P_2 n = 11	P_3 n = 5	P_4 n = 11
Age, yeas	50 (50-54)	60 (52-62)	62 (68-67)	66 (60-72) $p_1 = 0{,}0012$
AH (AFr)	6	3	0	0
AH/CHD (AFr)	2	8	5	11
NYHA I HF (AFr)	8	11	1	0
NYHA II HF (AFr)	0	0	2	5
NYHA III HF (AFr)	0	0	2	6
Preserved LV DF (AFr)	8	0	0	0
DD I (AFr)	0	10	0	0
DD II (AFr)	0	1	2	0
DD III (AFr)	0	0	3	0
DD n/d (AFr)	0	0	0	11
S_1, %	97 (97-98)	96 (96-97)	89 (86-94)	89 (80-91) $p_1 < 0{,}001$ $p_2 = 0{,}003$
S_2, %	95 (94-96)	93 (92-95)	79 (75-88)	80 (65-83) $p_1 < 0{,}001$ $p_2 = 0{,}003$
S_3, %	87 (85-90)	83 (81-87)	55 (48-73)	57 (34-63) $p_1 < 0{,}001$ $p_2 = 0{,}003$
M_1, %	3 (2-4)	4 (3-4)	11 (6-14)	11 (9-20) $p_1 < 0{,}001$ $p_2 = 0{,}003$
M_2, %	6 (5-7)	7 (5-8)	21 (12-25)	20 (17-35) $p_1 < 0{,}001$ $p_2 = 0{,}003$
M_3, %	14 (11-16)	17 (13-19)	45 (27-52)	43 (27-66) $p_1 < 0{,}001$ $p_2 = 0{,}003$
MLE, years	14,2 (13,1-15,9)	12,4 (11,5-14,6)	6,4 (5,6-9,4)	6,6 (4,2-7,4) $p_1 < 0{,}001$ $p_2 = 0{,}003$

AFr – absolute frequency; DF – diastolic function; DD I, II, III – diastolic dysfunction I (impaired relaxation), II (pseudonormalization) та III (restriction) type; DD n/d – DD not defined (in case of stabe AF); p_1 – statistical significance of difference P_1 vs. P_4; p_2 – statistical significance of difference P_2 vs. P_4.

Table 2

Parameters of structural and functional state of left ventricle in groups of comparison

	P_1 n = 8	P_2 n = 11	P_3 n = 5	P_4 n = 11
LAV_i, ml/m²	28,1 (22,2-32,6)	34,5 (31,3-39,0)	47,5 (43,2-56,3) p_3 = 0,012	57,2 (48,1-78,6) p_3 < 0,001 p_4 = 0,010
LVMM/BSA, g/m²	151,8 (128,0-167,9)	144,3 (132,9-153,4)	182,0 (172,0-182,8)	188,2 (169,8-211,3)
EF, %	60,7 (58,9-61,2)	59,2 (55,5-61,2)	47,8 (44,5-57,2)	53,1 (42,5-54,4) p_3 = 0,007
E/e_{sept}	7,1 (5,4-8,4)	7,6 (6,9-8,5)	21,9 (20,3-23,0) p_1 = 0,001 p_2 = 0,003	11,4 (7,2-15,2)
E/e_{lat}	4,9 (4,4-5,4)	6,2 (4,4-7,8)	15,3 (13,9-15,4) p_1 = 0,005	6,1 (5,3-9,6)
E/e_{av}	5,7 (4,9-6,2)	6,6 (5,7-7,5)	16,9 (16,5-19,6) p_1 < 0,001 p_2 = 0,012	8,1 (5,9-11,7)
e_{sept}, sm/s	9,4 (7,9-11,5)	6,9 (5,8-7,6)	3,9 (3,8-4,2) p_1 < 0,001	- *
e_{lat}, sm/s	13,7 (11,2-14,9)	8,5 (6,6-10,2)	4,6 (4,3-5,7) p_1 = 0,005	- *
e_{av}, sm/s	11,5 (10,8-12,1)	7,5 (6,9-8,9)	4,5 (4,2-4,8) p_1 < 0,001	- *

p_1 – statistical significance of difference P_1 vs. P_3; p_2 – statistical significance of difference P_2 vs. P_3; p_3 – statistical significance of difference P_1 vs. P_4; p_4 – statistical significance of difference P_2 vs. P_4; * - analyzed in case of sinus rhythm

Table 3

Statistical moments of polarization maps of erythrocytic suspension smears at different patterns of left ventricular remodeling

	P_1 n = 8	P_2 n = 11	P_3 n = 5	P_4 n = 11
Z_1	0,37 (0,29-0,41)	0,35 (0.32-0,40)	0,37 (0,34-0,47)	0,41 (0,39-0,44)
Z_2	0,220 (0,173-0,255)	0,260 (0,230-0,290)	0,290 (0,280-0,320)	0,325 (0,310-0,340) p_2 < 0,001
Z_3	0,265 (0,120-0,415)	0,390 (0,290-0,530)	0,640 (0,540-0,710) p_1 < 0,001	0,545 (0,470-0,620) p_2 = 0,012
Z_4	0,355 (0,160-0,505)	0,490 (0,430-0,590)	0,710 (0,690-0,880) p_1 < 0,001	0,730 (0,670-0,810) p_2 = 0,002

p_1 – statistical significance of difference P_1 vs. P_3; p_2 – statistical significance of difference P_1 vs. P_4.

Thus, the continuum of remodeling patterns of LV is characterized by the increase of frequency of constellation of AH/CAD in P_2 if compared with P_1 ($\chi^2 = 4.232$, df = 1, p = 0.040; the accurate Fisher's test p = 0,070) with its 100% frequency with P_3 and P_4; progressing of systolic and DD of LV; clinical manifestation of HF; the growth of anisotropy of the erythrocytic suspension in the form of the increase of the values of statistical moments of the 2^{nd}-4^{th} order of its laser images' polarization maps.

The average age of P_1 patients is statistically significantly lower than that of the other three patterns. This fact explains the observed statistically significant correlations Z_2-Z_4 with the age (r = 0.45, p = 0.007; r = 0,51, p = 0.002; r = 0.54, p = 0.001 respectively). Thus, to exclude the influence of the age factor, the analysis of correlations Z_2-Z_4 with parameters of structural and functional LV myocardium state was performed in the sampling, homogeneous by age (Tables 4-5).

Table 4

Matrix of correlation coefficients of statistical moments of 2^{nd}-4^{th} order with some parameters of structural and functional state of left ventricle (patterns 1-4), n = 19

	Z_2	Z_3	Z_4
EF	r = -0,52 p = 0,023	r =-0,54 p = 0,016	r = -0,64 p = 0,003
LVMM/BSA	r =0,44	r = 0,60 p = 0,007	r = 0,65 p = 0,003
E/e_{sept}	r =0,27	r = 0,63 p = 0,004	r = 0,57 p = 0,011
E/e_{av}	r =0,29	r = 0,50 p = 0,029	r =0,45

Table 5

Matrix of correlation coefficients of statistical moments of 2^{nd}-4^{th} order with some parameters of structural and functional state of left ventricle (patterns 1-3), n = 13

	Z_2	Z_3	Z_4
LAV_i	r = 0,65 0,016	r = 0,83 p = 0,001	r = 0,80 p = 0,001
E/e_{sept}	r = 0,39	r = 0,62 p = 0,024	r = 0,73 p = 0,005
E/e_{lat}	r = 0,38	r = 0,66 p = 0,014	r = 0,70 p = 0,007
E/e_{av}	r = 0,36	r = 0,64 p = 0,018	r = 0,72 p = 0,006
e_{sept}	r = -0,46	r = -0,58 p = 0,039	r = -0,63 p = 0,020
e_{av}	r = -0,39	r = -0,55 p = 0,050	r = -0,61 p = 0,028

Therefore, according to the correlation matrices data, the erythrocytic suspension anisotropy growth correlated with deterioration of the structural and functional state of LV.

Correlations with the survival parameters were performed both in the total and in homogeneous by age groups of patients under examination, as the age is a separate prognostic predictor in SHFM (Tables 6-8).

Table 6

Matrix of correlation coefficients of statistical moments of 2nd-4th order with parameters of prognosis (patterns 1-4), n = 35

	Z_2	Z_3	Z_4
S_1	r = -0,61 p < 0,001	r = -0,57 p < 0,001	r = -0,63 p < 0,001
S_2	r = -0,62 p < 0,001	r = -0,59 p < 0,001	r = -0,65 p < 0,001
S_5	r = -0,62 p < 0,001	r = -0,58 p < 0,001	r = -0,64 p < 0,001
M_1	r = 0,61 p < 0,001	r = 0,57 p < 0,001	r = 0,63 p < 0,001
M_2	r = 0,62 p < 0,001	r = 0,58 p < 0,001	r = 0,65 p < 0,001
M_5	r = 0,63 p < 0,001	r = 0,59 p < 0,001	r = 0,65 p < 0,001
MLE	r = -0,62 p < 0,001	r = -0,58 p < 0,001	r = -0,64 p < 0,001

Table 7

Matrix of correlation coefficients of statistical moments of 2nd-4th order (age corrected) with parameters of prognosis (patterns 1-4), n = 20

	Z_2	Z_3	Z_4
S_5	r = -0,57 p = 0,009	r = -0,67 p = 0,0013	r = -0,73 p = 0,0003
M_5	r = 0,62 p = 0,004	r = 0,70 p = 0,0006	r = 0,76 p = 0,00009
MLE	r = -0,58 p = 0,007	r = -0,67 p = 0,0011	r = -0,74 p = 0,0002

Table 8

Matrix of correlation coefficients of statistical moments of 2nd-4th order (age corrected) with parameters of structural and functional state of left ventricle (patterns 1-4), n = 20

	S_1	S_2	S_5	M_1	M_2	M_5	MLE
LVMM/ BSA	r = - 0,49 p = 0,033	r = - 0,46 p = 0,046	r = - 0,47 p = 0,041	r = 0,49 p = 0,033	r = 0,46 p = 0,046	r = 0,56 p = 0,014	r = -0,48 p = 0,032
E/e_{av}	r = -0,48 p = 0,034	r = -0,50 p = 0,028	r = - 0,49 p = 0,033	r = 0,48 p = 0,036	r = 0,50 p = 0,028	r = 0,471 p = 0,042	r = -0,53 p = 0,015

Thus statistically significant correlations were observed between three groups of parameters: survival, structural and functional LV myocardium state and statistical moments of the 2nd-4th order of coordinate distributions of ellipticity of polarization of laser images of the erythrocytic suspension smears. Here, the deterioration of the prognosis in the continuum of P_1 - P_4 correlated with both abnormality of structural and functional state of LV and growth of the erythrocytic suspension anisotropy.

As Z_2-Z_4 correlated with both the parameters of survival and of structural and functional LV state, they were selected for the analysis of association with the prognosis. For that the model of logistic regression was used in the following general form (3):

$$p = \frac{e^{\beta_0 + \beta_1 X}}{1 + e^{\beta_0 + \beta_1 X}} \quad (3)$$

where p – probability of belonging to one of the binary outcomes (0-1), e – base of natural logarithm (2.72), β_0 – constant, β_1 – coefficient, X – predictor (Z_2-Z_4).

Belonging of each patient to one of two clusters according to the survival rates was used as a binary outcome. For that the group of patients under study was divided into clusters by relation to Me of such survival parameters as B_5, C_5 and MLE (Table 9).

Table 9

Survival rates in clusters of comparison

	Above or equal Me	Below Me
S_5, %	86 (83-88) n = 19	57 (47-73) n = 16
M_5, %	40 (24-53) n = 19	14 (11-16) n = 16
MLE, years	13,8 (12,4-14,9) n = 18	6,6 (5,4-9,2) n = 17

Therefore, in the suggested regressive models the probability of belonging to one of survival clusters due to the predictors Z_2-Z_4 was calculated (Tables 10-11).

Table 10

Parameters of logistic regression models for S_5 and MLE clusters as outcomes and Z_2-Z_4 as predictors

	Constant (β_0)	Z	p_1	Coeffi-cient (β_1)	Z-sta-tis-tics	p_2	χ^2 Hosmer-Lemeshow test	p_3	% CP
Z_2	-9,5625	-2,98	0,003	34,2011	3,01	0,003	4,347	0,739	84,0
Z_3	-5,1688	-2,74	0,006	10,7986	2,86	0,004	3,902	0,866	85,0
Z_4	-7,8789	-2,86	0,004	3,864	2,94	0,003	3,864	0,869	90,2

p_1, p_2, p_3 – levels of statistical significance for β_0, β_1 and χ^2 respectively; CP – concordant pairs.

Table 11

Parameters of logistic regression models for M_5 and MLE clusters as outcomes and Z_2-Z_4 as predictors

	Constant (β_0)	Z	p_1	Coeffi-cient (β_1)	Z-sta-tis-tics	p_2	χ^2 Hosmer-Lemeshow test	p_3	% CP
Z_2	-6,1734	-2,53	0,011	23,7569	2,66	0,008	8,108	0,323	76,7
Z_3	-3,4866	-2,47	0,013	8,3677	2,81	0,005	5,271	0,728	80,3
Z_4	-4,9982	-2,67	0,008	9,2014	2,91	0,004	4,436	0,816	85,3

p_1, p_2, p_3 – levels of statistical significance for β_0, β_1 and χ^2 respectively; CP – concordant pairs.

Thus, the presented above models of logistic regression quite adequately describe the association of Z_2-Z_4 with the clusters of survival parameters. This testifies to their prognostic significance and possibility of usage together with the clinical, laboratory and instrumental data in the system of individualized complex assessment of AH and CAD patients prognosis.

4. CONCLUSIONS

1. Continuum of LV remodeling patterns of AH and CHD patients is characterized by worsening of survival parameters, deterioration of structural and functional state of LV myocardium and growth of the erythrocytic suspension anisotropy in the form of increase of the value of statistical moments of the 2^{nd}-4^{th} order of polarization maps of its laser images.

2. The increase of the values of statistical moments of the 2^{nd}-4^{th} order of polarization maps of the erythrocytic suspension laser images correlates with deterioration of structural and functional state of LV

myocardium and is associated with unfavorable prognosis for AH and CHD patients in LV remodeling continuum.

In perspective, we consider it worthy to study the relations of optical and other properties of erythrocytes (deformability, catecholamine-binding function, etc.) at AH and CHD at different stages of cardiovascular continuum and in the context of metabolic disorders.

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