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## FEATURES OF MICROCIRCULATORY DYSFUNCTION ACCORDING TO WAVLET ANALYSIS LASER DOPPLER FLOWMETRY IN PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE AND CONCOMITANT DIFFUSE LIVER DISEASES

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**Aim.** To determine the features of microcirculatory dysfunction and in patients with chronic ischemic heart disease, depending on the presence of concomitant diffuse liver disease. **Materials and methods.** We performed a prospective study on the basis of MC «Doctor Vera», as well as in the diagnostic department of Medbud Clinic between 2009 and 2019. A total of 187 patients were examined. Patients' blood flow was assessed by transthoracic echocardiography, wavelet analysis laser Doppler flowmetry (LDF). **Results.** In the analysis of indicators of microcirculatory dysfunction in patients with ischemic heart disease, statistically significant deterioration of wavelet analysis laser Doppler flowmetry was determined. In patients with ischemic heart disease and left ventricular ejection fraction < 40 %, indicators of wavelet analysis LDF were significantly lower. We also found that the severity of diffuse liver disease significantly disrupts peripheral blood flow ( $P < 0.05$ ). **Conclusions.** The results of intracardiac hemodynamics, microcirculatory dysfunction were first presented. In patients with isolated ischemic heart disease as the left ventricular EF decreased, a significant decrease in capillary blood flow was observed as a result of deterioration of central hemodynamics, development of atherosclerotic vascular changes, as well as an increase in their vascular tone. We have proved that in the presence of DLD in patients with ischemic heart disease and EF < 40 %, the degree of increase in peripheral resistance and impaired venous outflow were more pronounced due to the depletion of vasoactive substances production, impaired their excretion by hepatocytes due to irreversible morpho-functional changes in liver at the stage of decompensation of HF, severe fibrosis, the formation of regeneration nodes. In patients with LC, the most severe disorders of peripheral blood flow were determined according to the data of the digital capillaroscopy, which testifies to the influence of the degree of liver damage on the state of microcirculation.

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**Key words:** ischemic heart disease; systolic and diastolic dysfunction of left ventricular; wavelet analysis; laser Doppler flowmetry; diffuse liver diseases; microcirculatory dysfunction.

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**Introduction.** Microcirculatory disorders are characteristic of patients with ischemic heart disease (IHD), diffuse liver disease (DLD), but to date, the issue of clinical manifestations and microcirculatory disorders in these patients has not been sufficiently studied.

**Aim.** To determine the features of the development of microcirculatory disorders according to wavelet analysis of LDF in patients with chronic ischemic heart disease, depending on the presence of concomitant diffuse liver disease.

**Materials and methods.** We conducted open prospective investigation in the Medical center “Doctor Vera” and diagnostic department of Medbud Clinic from 2009 till 2019. Patients were selected in the study according to the criteria of inclusion: presence of IHD and DLD. There was one more group with 30 healthy volunteers. The investigation was conducted according to the standards of Good Clinical Practice, Ukrainian medical law and all patients signed informed agreement. 187 pa-

tients were included in the study: 34 women and 154 men from 18 to 85 years old (average age was  $46.1 \pm 17.4$ ). There were three groups in our study.

The first group included 55 patients with chronic IHD and with chronic heart failure (CHF) I–II B stages, I–IV functional classes (NYHA), average age  $61.5 \pm 12.8$  and there were 16 women (29 %) with ejection fraction of the left ventricle (EF) ( $44.2 \pm 8.6$ ) % (table 1). The average duration of IHD was ( $8.2 \pm 5.7$ ) years.

**Table 1. Indicators of wavelet analysis laser Doppler flowmetry in patients with ischemic heart disease depending on the status of systolic and diastolic function ( $M \pm SD$ )**

Data of LDF $M \pm SD$ (perfusion units)	EF > 40 % E/A > 1.0 (n = 9)	EF > 40 % E/A < 1.0 (n = 5)	EF < 40 % E/A > 1.0 (n = 10)	EF < 40 % E/A < 1.0 (n = 6)	Healthy volunteers (n = 30)
A <sub>max</sub> E (p.u.)	$0.19 \pm 0.04^{*\S}$	$0.20 \pm 0.04^*$	$0.18 \pm 0.07^*$	$0.18 \pm 0.08^*$	$0.33 \pm 0.15$
A <sub>max</sub> N (p.u.)	$0.20 \pm 0.05^*$	$0.23 \pm 0.17$	$0.20 \pm 0.05^*$	$0.19 \pm 0.04^*$	$0.32 \pm 0.14$
A <sub>max</sub> M (p.u.)	$0.18 \pm 0.06^*$	$0.20 \pm 0.06^{*\dagger}$	$0.20 \pm 0.08^*$	$0.18 \pm 0.04^*$	$0.47 \pm 0.18$
A <sub>max</sub> R (p.u.)	$0.13 \pm 0.05^{\S\dagger}$	$0.32 \pm 0.11^*$	$0.20 \pm 0.07^*$	$0.15 \pm 0.07^\dagger$	$0.15 \pm 0.05$
A <sub>max</sub> C (p.u.)	$0.19 \pm 0.04$	$0.34 \pm 0.14^{*\dagger}$	$0.20 \pm 0.04$	$0.22 \pm 0.04$	$0.18 \pm 0.10$
Shunting indicator (SI)	$1.42 \pm 0.19^*$	$1.54 \pm 0.40^*$	$1.37 \pm 0.16^*$	$1.35 \pm 0.20$	$1.09 \pm 0.35$

\*P < 0.05 comparing to the healthy volunteers.

§P < 0.05 comparing to the group with different EF.

†P < 0.05 comparing to the patients with different E/A at the same EF.

The first group was divided into subgroups A and B depending on the presence (1B) or absence (1A) of the DLD. The subgroup 1B included the following DLD: 5 (20 %) patients with chronic toxic hepatitis (CTH), 14 (56 %) – nonalcoholic steatohepatitis (NASH), 5 (20 %) – chronic viral hepatitis (CVH) B and C (CVHB, CVHC), 3 (12 %) – liver cirrhosis (LC) A–B classes according to Child-Pugh, 3 (12 %) – cryptogenic hepatitis. More than one third of the patients with IHD had myocardial infarction. All the patients had concomitant arterial hypertension. Patients with NASH had insulin-independant type 2 diabetes mellitus.

The second group included 102 patients with DLD, average age was ( $37.3 \pm 15.2$ ) years: 12 patients with LC, average age was ( $45.1 \pm 9.2$ ) years; 43 patients with CVH: 6 women, average age was ( $31.8 \pm 8.9$ ) years, 12 patients with CVHB, 24 patients with CVHC, 4 patients with CVHB + C, 2 patients with viral hepatitis Epstein – Barr, 1 patient with CVH TTV; 21 patients with CTH of mixed etiology, especially alcoholic, average age ( $42.7 \pm 12.6$ ) years; 26 patients with NASH, average age ( $40.8 \pm 10.0$ ) years. We also analysed the data of the patients in the second group according to the stages of liver diseases: subgroup A – 48 patients with minimal cytolytic syndrome and cholestasis (elevation of alaninaminotransferase (ALT) less than in 5 times; bilirubin was less than 100 mcmmol/l); subgroup B – 42 patients with moderate syndrome of cytolysis and cholestasis (elevation of ALT in 5–10 times, bilirubin from 100 to 200 mcmmol/l); subgroup B – 12 patients with LC.

The third group included 30 healthy volunteers (8 women – 25.7 % and 22 men – 74.3 %), average age ( $33.5 \pm 8.4$ ) years.

Transthoracic echocardiography (echoCG) was conducted on the device HDI 11XE Philips according to the general methodology [13] with measurement in 2D-mode of wall thickness of the right ventricle (Trv), posterior wall of the LV (Tlv), intraventricular septum (Tivs), short-axis size of the left atrium (LA), end diastolic volume (EDV) of LV by Simpson, its EF and also short-axis size of the RV in basal chamber – Drv(s), diameter of vena cava inferior (VCI). Diastolic filling of the LV was evaluated according to the ratio of transmitral flow velocity in the period of rapid filling and in systolic phase of the LA (E/A), time of

decreasing of early diastolic filling velocity – deceleration time (DT) and duration of the period of left ventricular isovolumic relaxation time (IVRT). Systolic pressure of the pulmonic artery (SPPa) was evaluated by the speed of tricuspid regurgitation flow [13].

Laser Doppler flowmetry (LDF) – was conducted on the device Laser Doppler flowmetr LAKK-02 (SPE “Lasma”, Moscow) by conventional method [4, 15, 16, 18]. LDF based on optical sensing of tissues by monochromatic signal and analysis of frequency spectrum of signals reflected from erythrocytes having Doppler frequency shift [12, 15].

The signal reflected from the erythrocytes has a Doppler frequency shift relative to the scanning beam. The depth of optical sensing of tissues depends essentially on the wavelength of the laser source. For red radiation (632 nm), it does not exceed 1mm. Signal recorded during LDF characterizes blood flow in microvessels in a volume of 1–1.5 mm<sup>3</sup> tissue [4, 12, 14].

In human skin, LDF provides integral information on a very large number of erythrocytes, about  $3.4 \cdot 10^4$  /mm<sup>3</sup>, which are simultaneously in the area of tissue probing. The patient's blood flow is recorded at rest for 8 minutes after a 15-minute adaptation period. Functional test with occlusion of the brachial artery is performed.

The occlusal test (OT) is realized by compressing for 1–3 min the corresponding area of the limb with the tonometer cuff so as to cause a stop of blood flow and, accordingly, ischemia in the study area.

After cessation of the occlusion, the blood flow resumes and develops reactive post-occlusive hyperemia, which is manifested in an increase in the microcirculation index to a value that exceeds the initial level of indicator of microcirculation (IM) with subsequent decline to the initial level.

The physiological role of a compression test is manifested in stop blood supply in the shoulder arteries and respectively in changes blood circulation in the tissues. In the majority of cases the blood pressure and the rate of blood circulation in the vessels of microcirculation are changed. At the time of decompression of blood, arterial blood flow and reactive hyperemia appears with maximum blood levels of blood vessels of microcirculation. Change blood pressure is the minimum hour of compression up to the maximum time of the reactive characteristic is the entire range of capacities of the blood pressure.

When a given test is carried out, an estimate of the “biological zero” indicator (indicator of microcirculation for the incidence of arterial congestion) and increased reserve of the microcirculatory channel according to the increase in the indicator of microcirculation is observed during reactive post-inclusive hyperemia.

According to experimental studies, post-exclusion reactive hyperemia is a neurogenic reaction, which is realized mainly through the release of neuropeptide KGRP (cocalcigenin) and neuronal nitric oxide (NO), secreted by afferent nociceptive C-fibers. These factors induce NO synthesis by the endothelium, which in turn, by vasodilating the vasculature by affecting vascular smooth muscle [3, 4, 7].

Determined the baseline state of microcirculation by indicator of microcirculation (IM) and capillary blood flow reserve (CBFR) during OT.

Previously, in this study, all patients with the use of an occlusive test sample identified 4 variants of hemodynamic types of microcirculation (HTM). In particular: normocirculatory, hyperemic, spastic, stasic.

Normocirculatory HTM is characterized by an initial magnitude of IM = 4.5 – 6.5 p.u., with a normoreactive type of response to arterial occlusion, CBFR = 200 – 300 %. Hyperemic HTM is characterized by an increase in blood flow to the microcirculatory bed with an initial IM value > 6.5 p. u. in OT, the type of response to arterial occlusion is hyperreactive (reducing IM by more than 3.2 p. u.). CBFR is always below 200 %. Spastic HTM is characterized by a decrease in blood flow to

the microcirculatory bed due to spasm of precapillary sphincters. initial IM reduced  $< 4.5$  p. u., and at OT the type of blood flow for arterial occlusion is reactive (decrease in IM during occlusion by less than 1.5 p. u.); CBFR  $> 300$  %. Stasic HTM is noted at decrease in speed and stasis of blood flow at the level of the capillary unit, as well as at the level of the post-capillary unit- venules and postcapillaries. Thus IM  $< 4.5-6.5$  p. u., the degree of decrease in IM depends on the severity of the phenomena of blood stasis and rheological disorders (aggregation of blood elements, sweet phenomenon); CBFR  $< 200$  %. Type of blood flow to arterial occlusion – areactive. This type of microcirculation is noted in paresis of vessels of inflow and disturbance of outflow [4].

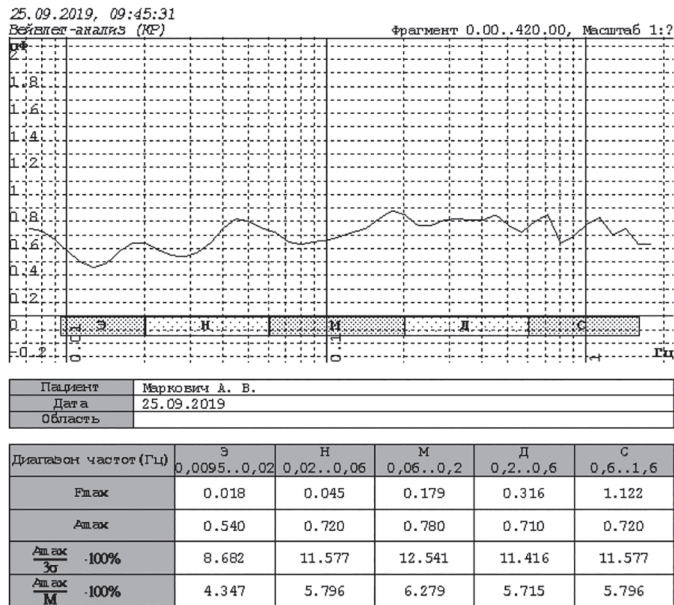
### Функциональные пробы



Fig. 1. Occlusal test. Normocirculatory hemodynamic type of microcirculation

In wavelet analysis, the following components were identified:

$A_{max}C$  – maximum amplitude of cardiac flaxmotions – oscillations of the capillary wall caused by a contraction of the heart form a peak in the frequency range by synchronous pulse oscillation.  $A_{max}R$  – maximum amplitude of respiratory fluxmotions – in the frequency range of the respiratory function of the oscillation of the capillary wall form a respiratory peak.  $A_{max}M$  – maximal amplitude of myogenic flaxmotions and  $A_{max}N$  amplitude of neurogenic flaxmotions – myogenic and – neurogenic activity of precapillary vasomotors are detected with maximum frequencies in the range of 0.02–0.16 Hz.  $A_{max}E$  is the maximum amplitude of endothelial fluxmotions – the slowest oscillations in the microcirculatory system, which are synchronous and dependent on the activity of endothelial cells due to the secretion of various compounds, in particular nitric oxide. SI – shunting indicator of AV – shunt that indicates the state of nutritional blood flow.



**Fig. 2.** Wavelet-analysis of laser Doppler flowmetry – curves, which graphically depict the dependence of the amplitudes of these types of oscillations on their frequencies (this wavelet analysis of healthy volunteers. Indicators are within normal limits)

Endothelium dependent vasodilatation (EDV) and endothelium-independent vasodilatation (EIDV) by D. S. Celermajer and co-authors method was conducted with ultrasound system HD 11 (Philips MS) and lineal transducer with frequency 3–12 MHz according to its methodology [11, 12].

Humoral marker of endothelial dysfunction Willebrand factor (Wf) was identified with agglutination method with ristomycin and control with ELISA method on the device Stat Fax 303.

Laboratory marker of endothelial dysfunction (ED) such as circulating endothelial cells (CEC) were identified with J. Hladovec, Petrishev, V. V. Syvak In this method adrenalin was used instead of adenosine phosphate which reduced the cost of investigation [9].

Statistical analyses was made with Statistica for Windows 7.0 (Statsoft, USA). Distribution of the values was expressed as median, mean and Shapiro-Wilk criterion. Comparing groups was held with Vilkokson – Mann – Witney criterion and Student's *t*-test. Reliability of nonparametric data discrepancies in groups (including follow-up period) was made with Chi-square criterion. Correlation analyses was made with Pearson's correlation criterion. The discrepancies were statistically significant at  $P < 0.05$ .

**Results and discussion.** According to the recommendations of the Ukrainian association of cardiologists of diagnosis, treatment and prevention of chronic heart insufficiency (CHI) in adults (2017) we divided our patients into two groups: group 1 with normal EF of the LV systolic function ( $EF_{lv} > 40\%$ ) and group 2 with reduced EF ( $EF_{lv} < 40\%$ ). For additional evaluation of the stage of diastolic dysfunction of LV we created subgroups with E/A more and less than 1 in every group. We evaluated the fact that  $E/A > 1.0$  at  $EF_{lv} < 40\%$  was related to the pseudonormal/restrictive type of transmitral flow and in case of  $EF_{lv} > 40\%$   $E/A > 1.0$  better diastolic filling of LV was performed comparing the patients with  $E/A < 1.0$  (diastolic dysfunction of the LV by relaxation disorder type). Part of the patients with concomitant DLD among the patients with  $EF_{lv} > 40\%$  was 41% and among the patients with  $EF_{lv} < 40\%$ –50%.

The results of the analysis of indicators of intracardiac hemodynamics were presented in our previous scientific publications [16], so in this article we reflect the state of microcirculatory dysfunction according to wavelet analysis of LDF.

In the analysis of wavelet analysis in patients with IHD (Table 1) revealed a decrease in  $A_{\max} E$  (p. u.),  $A_{\max} N$  (p. u.),  $A_{\max} M$  (p. u.), while increasing the value of  $A_{\max} R$  (p. u.) in the group of patients with an ejection fraction of more than 40 %, with impaired left ventricular relaxation. This indicates a decrease in capillary blood flow, due to an increase in myotonus and neurotonus of the capillaries, as well as a decrease in venular outflow in patients with IHD with  $EF > 40\%$  and  $E/A < 1.0$ , due to the development of heart failure [4, 6].

In this case, the degree of these changes is greater in patients with  $EF < 40\%$  compared with patients with preserved systolic function (lower values of  $A_{\max} E$ ,  $A_{\max} R$  than in  $EF > 40\%$  indicate worse peripheral blood flow in patients with IHD with low ejection fraction) and the lowest wavelet analysis rates were observed in the group of patients with reduced  $EF$  and  $E/A$  less than 1.0.

In the analysis of indicators  $A_{\max} E$ ,  $A_{\max} N$ ,  $A_{\max} M$ , as well as  $A_{\max} R$ , a tendency to increase the parameters of microcirculation  $A_{\max} E$ ,  $A_{\max} N$ ,  $A_{\max} M$ , as well as a significant increase in  $A_{\max} R$ , indicating “pseudonormalization” of the above indicators, microcirculation, that there is a cyclical course of changes of microcirculation depending on the state of systolic and diastolic dysfunction of the left ventricle with IHD identical to the changes inherent in the development of diastolic dysfunction of the left ventricle.

A worse condition of  $A_{\max} E$  in patients with low  $EF$  and  $E/A$  greater than 1.0 is associated with a deterioration of the microcirculation state than in relatively preserved  $EF$  due to a number of researchers [2, 5, 6, 10] with a decrease in cardiac output and blood volume per capillary, as well as with increased peripheral resistance due to the activation of SAS and RAAS, as well as hyperproduction of  $TNF-\alpha$ , endothelin, angiotensin II, thromboxane and other vasoconstrictors [3, 4, 7, 14].

Among patients with IHD with  $EF > 40\%$  at  $E/A < 1.0$ , higher values of  $A_{\max} M$ ,  $A_{\max} C$ ,  $A_{\max} R$  were observed, which indicates a more pronounced violation of venular outflow in patients with impaired LV relaxation.

Thus, in the complex analysis of indicators of intracardiac hemodynamics, microcirculation and endothelial function in patients with IHD revealed their dependence not only on the magnitude of  $EF$  (more/less than 40 %), but also on the state of its diastolic filling. In this case, the dependence of indicators ( $A_{\max} E$ ,  $A_{\max} N$ ,  $A_{\max} M$ ) on the nature of the filling of the LV was observed already at  $EF$  more than 40 %.

The results of the study of the microcirculation state by the LDF method in patients with IHD and in patients with DLD, as well as in their combination are given in table 2.

Table 2. Indicators of wavelet analysis laser Doppler flowmetry in patients with ischemic heart disease and diffuse liver diseases ( $M \pm SD$ )

Data of LDF $M \pm SD$ (perfusion units)	Groups			
	IHD ( $n = 30$ )	IHD + DLD ( $n = 25$ )	DLD ( $n = 102$ )	Healthy volunteers ( $n = 30$ )
$A_{\max} E$ (p.u.)	$0.18 \pm 0.03^{*\wedge}$	$0.24 \pm 0.07^*$	$0.25 \pm 0.14^{*\#}$	$0.33 \pm 0.15$
$A_{\max} N$ (p.u.)	$0.21 \pm 0.06^*$	$0.21 \pm 0.03^*$	$0.26 \pm 0.17$	$0.32 \pm 0.14$
$A_{\max} M$ (p.u.)	$0.20 \pm 0.06^{*\wedge}$	$0.17 \pm 0.04^*$	$0.26 \pm 0.17^{*\#}$	$0.47 \pm 0.18$
$A_{\max} R$ (p.u.)	$0.19 \pm 0.09^\wedge$	$0.10 \pm 0.03^*$	$0.18 \pm 0.15$	$0.15 \pm 0.05$
$A_{\max} C$ (p.u.)	$0.23 \pm 0.09^\wedge$	$0.16 \pm 0.04$	$0.18 \pm 0.11^\#$	$0.18 \pm 0.10$
Shunting indicator (SI)	$1.36 \pm 0.27^*$	$1.24 \pm 0.20$	$1.28 \pm 0.27^*$	$1.09 \pm 0.35$

\*  $P < 0.05$  comparing to the healthy volunteers.

$\wedge P < 0.05$  compared to a subgroup IHD with DLD.

$\# P < 0.05$  compared to a subgroup IHD.

In patients with IHD without DLD, the lowest values of  $A_{\max}E$  were observed, when compared with healthy and patients of all groups, which is associated with a decrease in production of nitric oxide on the one hand, as well as activation of the sympatho-adrenal system and renin angiotensin aldosterone system (RAAS) of patients with IHD on the other [1, 18, 19].

$A_{\max}N$  and  $A_{\max}M$  were also lower compared with healthy, indicating an increase in neurotonus and myotonus in patients with IHD.

IS was larger in the group of patients with IHD, indicating a decrease in nutritional blood flow when compared with healthy, which is consistent with the results of other studies [16]. In patients with DLD, a moderate decrease in  $A_{\max}E$  and  $A_{\max}M$  is observed, with an increase in IS, indicating moderate endothelial dysfunction, an increase in the myotonic tone of precapillary sphincters, and a slight decrease in nutritional blood flow when compared with healthy volunteers.

The combination of IHD and DLD showed the greatest decrease in  $A_{\max}M$ ,  $A_{\max}R$ , indicating a deterioration of capillary blood flow due to increased myotonus of the precapillary sphincters, increased venular outflow, due to the production of proinflammatory cytokines (IL 2, 6, 8, TNF $\alpha$ ) violation of their utilization by the affected liver – on the other (which explains the absence of a pronounced peripheral spasm, as well as violation of the venular outflow). The moderate decrease in  $A_{\max}E$  (similar to the  $A_{\max}E$  value in patients with DLD) was observed, possibly associated with a decrease in the activity of the L-arginine NO system [7, 8, 10].

In patients with DLD compared with healthy volunteers there was a significant decrease in  $A_{\max}E$ ,  $A_{\max}M$ , as well as an increase in SI. Endothelial dysfunction is less pronounced than in patients with IHD, and similar in value to patients with IHD + DLD, the precapillary myotonus was greater than in healthy but less than in patients with IHD, as well as IHD + DLD. Passive mechanisms of regulation of microcirculation did not differ from the control group, but the nutritional blood flow was worse than in healthy volunteers.

At EF > 40 %, in patients with IHD in the presence of DLD, a smaller value of  $A_{\max}M$ ,  $A_{\max}R$ ,  $A_{\max}C$  was observed, indicating an increase in myotonic tone of the arterioles and a slight (relative) narrowing of the precapillary sphincters (table 3). This may be due to changes in liver function with increased concentrations of vasoconstrictors (thromboxane A2, endothelin I, angiotensin II), and decreased utilization of their liver.

**Table 3. Data of wavelet analysis laser Doppler flowmetry (perfusion units) in pts with ischemic heart diseases depending on the availability of companions diffuse liver diseases and ejection fraction ( $M \pm SD$ )**

Data of LDF $M \pm SD$ (perfusion units)	IHD EF > 40 %		IHD EF < 40 %		Healthy volunteers ( $n = 30$ )
	IHD ( $n = 13$ )	without DLD ( $n = 14$ )	IHD ( $n = 12$ )	without DLD ( $n = 16$ )	
$A_{\max}E$ (p. u.)	$0.20 \pm 0.05^*$	$0.20 \pm 0.03^*$	$0.29 \pm 0.06^\dagger$	$0.18 \pm 0.03^*$	$0.33 \pm 0.15$
$A_{\max}N$ (p. u.)	$0.19 \pm 0.03^*$	$0.20 \pm 0.03^*$	$0.23 \pm 0.05^*$	$0.19 \pm 0.07^*$	$0.32 \pm 0.14$
$A_{\max}M$ (p. u.)	$0.15 \pm 0.04^{\dagger*}$	$0.21 \pm 0.08^*$	$0.20 \pm 0.03^*$	$0.19 \pm 0.05^*$	$0.47 \pm 0.18$
$A_{\max}R$ (p. u.)	$0.18 \pm 0.03^\dagger$	$0.23 \pm 0.13$	$0.12 \pm 0.02^\dagger$	$0.17 \pm 0.03$	$0.15 \pm 0.05$
$A_{\max}C$ (p. u.)	$0.10 \pm 0.03^\dagger$	$0.26 \pm 0.13$	$0.13 \pm 0.04^{\dagger*}$	$0.21 \pm 0.05^*$	$0.18 \pm 0.10$
Shunting indicator (SI)	$1.25 \pm 0.25$	$1.48 \pm 0.30$	$1.22 \pm 0.10^*$	$1.36 \pm 0.18$	$1.09 \pm 0.35$

\*P < 0.05 comparing to the healthy volunteers.

†P < 0.05 comparing to the pts with IHD without DLD with similar EF.

Among patients with IHD with EF < 40 % in the presence of concomitant DLD, lower values of  $A_{\max}R$  and  $A_{\max}C$  are noted – a decrease in the influence of passive

mechanisms of regulation of microcirculation, with activation of active mechanisms (a significant increase in  $A_{\max} E$ , as well as a tendency to increase  $A_{\max} N$ ,  $A_{\max} M$ ).

That is, the relative expansion of precapillary sphincters occurs due to a decrease in myotonus and neurotonus, caused on the one hand by a vasoconstrictor effect (absence/reduction of release of nitric oxide in response to acetylcholine release), depletion of cytokine production with vasoconstrictor effect (thromboxane A2, endothelin 1, etc.), increased production of liver inflammatory factors with vasodilating effect (TNF $\alpha$ , IL1, 6, 8, Endothelin 1, etc.), on the other hand, increasing the concentration of asymmetric dimethylarginine (ADMA) [3].

The analysis of LDF indices in patients of the third group confirms the significant effect of DLD on microcirculation. When comparing LDF data in patients with DLD of different etiology, changes in the value of wavelet analysis are less pronounced in CTH than in viral hepatitis and NASH and in LC (table 4).

**Table 4. Data of wavelet analysis laser Doppler flowmetry (perfusion units) in pts with diffuse liver diseases of different etiology ( $M \pm SD$ )**

Data of wavelet analysis (perfusion units)	LC (n = 12)	CVH (n = 43)	CTH (n = 21)	NASH (n = 26)	Healthy volunteers (n = 30)
$A_{\max} E$ (p. u.)	0.17 $\pm$ 0.10*	0.26 $\pm$ 0.17*	0.34 $\pm$ 0.19	0.27 $\pm$ 0.05^	0.33 $\pm$ 0.15
$A_{\max} N$ (p. u.)	0.26 $\pm$ 0.09	0.29 $\pm$ 0.18	0.28 $\pm$ 0.12	0.24 $\pm$ 0.09	0.32 $\pm$ 0.14
$A_{\max} M$ (p. u.)	0.19 $\pm$ 0.11*	0.27 $\pm$ 0.18*	0.25 $\pm$ 0.11*^	0.44 $\pm$ 0.14#^	0.47 $\pm$ 0.18
$A_{\max} R$ (p. u.)	0.16 $\pm$ 0.04	0.24 $\pm$ 0.20	0.13 $\pm$ 0.03	0.22 $\pm$ 0.11*	0.15 $\pm$ 0.05
$A_{\max} C$ (p. u.)	0.10 $\pm$ 0.03*	0.25 $\pm$ 0.14^	0.16 $\pm$ 0.08^	0.21 $\pm$ 0.11^	0.18 $\pm$ 0.10
Shunting indicator	1.60 $\pm$ 0.63*	1.17 $\pm$ 0.52	1.12 $\pm$ 0.28^	0.53 $\pm$ 0.15*†	1.09 $\pm$ 0.35

\*P < 0.05 comparing to the healthy volunteers.

^P < 0.05 comparing to the pts with liver cirrhosis.

†P < 0.05 comparing to the pts with chronic virus hepatitis.

#P < 0.05 comparing to the pts with на chronic toxic hepatitis.

The data obtained indicate a less pronounced violation of cytomicroarchitectonics (by  $A_{\max} M$ ), as well as blood flow velocity in the arterial and venous capillaries, with toxic hepatitis, compared with viral hepatitis NASH and LC. Patients with CTH experience an increase in myotonic tone more than with CVH and NASH, but less than in patients with LC.

Patients with viral hepatitis showed a greater impairment of endothelial function by  $A_{\max} E$ , when compared with controls and other patients (except LC group), with marked deterioration of venular outflow (by  $A_{\max} R$ ), an increase in myotone, slightly less than in patients with CTH. In patients with NASH there is an increase in the value of  $A_{\max} R$ , as well as a decrease in IS, this figure was the lowest in gr. NASH. When compared to the CTH group, more  $A_{\max} M$  was observed.

Decreased endothelial function and increased peripheral resistance due to paresis of precapillary sphincters (by indicators  $A_{\max} E$ ,  $A_{\max} M$  and  $A_{\max} C$ ) in patients with LC compared with patients with CTH and CVH. IS was the highest in the LC group, that is, the nutritional blood flow was the worst in the LC patients.

In the CTH and NASH groups, the  $A_{\max} E$  was the highest, probably on the one hand, due to the overproduction of nitric oxide, as well as the proinflammatory cytokines with vasodilating activity (I11, I16, I18) on the one hand, which causes vasodilation of the precapillaries, which in turn on the other hand with impaired liver utilization of substances such as glucagon, estrogens, adrenomedulin, prostaglandins, adenosine, bile acids and the like [3, 7, 8].

In general, by most indicators, the degree of hemodynamic abnormalities was highest in liver cirrhosis (significant changes in wavelet analysis).



At DLD of minimum gravity changes of values of active and passive mechanisms of regulation of microcirculation are less expressed, than at LC (table 5).

**Table 5. Indicators of wavelet analysis laser Doppler flowmetry in patients with diffuse liver diseases with different severity of liver damage ( $M \pm SD$ )**

Data of wavelet analysis LDF (perfusion units)	LC (n = 12)	DLD with severe degree of damage (n = 18)	DLD with moderate degree of damage (n = 20)	DLD with minimal degree of damage (n = 52)	Healthy volunteers (n = 30)
$A_{\max}E$ (p. u.)	$0.17 \pm 0.10^*$	$0.14 \pm 0.05^*$	$0.38 \pm 0.18^{\wedge\dagger}$	$0.27 \pm 0.10^{\wedge\dagger}$	$0.33 \pm 0.15$
$A_{\max}N$ (p. u.)	$0.26 \pm 0.09$	$0.12 \pm 0.12^{\wedge*}$	$0.33 \pm 0.06^{\dagger}$	$0.25 \pm 0.12^{\dagger}$	$0.32 \pm 0.14$
$A_{\max}M$ (p. u.)	$0.19 \pm 0.11^*$	$0.14 \pm 0.14^*$	$0.31 \pm 0.07^{\wedge\dagger*}$	$0.37 \pm 0.17^*$	$0.47 \pm 0.18$
$A_{\max}R$ (p. u.)	$0.16 \pm 0.04$	$0.08 \pm 0.02^{\wedge*}$	$0.24 \pm 0.11^{\dagger*}$	$0.17 \pm 0.10^{\#}$	$0.15 \pm 0.05$
$A_{\max}C$ (p. u.)	$0.10 \pm 0.03^*$	$0.16 \pm 0.04^{\wedge}$	$0.28 \pm 0.17^{\wedge}$	$0.21 \pm 0.10^{\wedge}$	$0.18 \pm 0.10$
Shunting indicator	$1.60 \pm 0.63^*$	$0.94 \pm 0.29$	$1.15 \pm 0.18$	$0.71 \pm 0.30$	$1.09 \pm 0.35$

\*  $P < 0.05$  comparing to the healthy volunteers.

$\wedge$   $P < 0.05$  comparing to the pts with liver cirrhosis.

$\dagger$   $P < 0.05$  comparing to the pts with DLD with severe degree of damage.

$\#$   $P < 0.05$  comparing to the pts with DLD with moderate degree of damage.

This indicates less impaired venular outflow, decreased tone of the precapillary sphincters, and a slight increase in capillary blood flow with minimal severity of liver damage compared with liver cirrhosis.

In patients with moderate syndrome of cytolysis and/or cholestasis revealed a moderate disturbance of venular outflow by  $A_{\max}R$  and a decrease in peripheral resistance of the precapillaries due to a decrease in myotonic tone by indicators ( $A_{\max}M$  and  $A_{\max}C$ ). This is due to the overproduction of proinflammatory cytokines (IL 2, 6, 8, TNF $\alpha$ ) in DLD patients with moderate and minimal cytolysis and cholestasis syndrome [7, 8, 17].

The phase changes of  $A_{\max}E$ ,  $A_{\max}N$ ,  $A_{\max}M$ ,  $A_{\max}R$  and IS depending on the severity of the liver lesions were interesting. With minimal liver damage, a decrease in the indicators of active mechanisms of regulation of microcirculation was observed, as well as an increase in the values of passive mechanisms of regulation of microcirculation. In moderate syndrome of cytolysis and cholestasis increased the values of  $A_{\max}E$ , IS and  $A_{\max}N$  (increased intensification of the system L-arginine NO, decreased neurotonus, decreased nutritional blood flow), as well as  $A_{\max}R$  and  $A_{\max}C$  (deterioration of the venular outflow and enlargement of maxima) started to decline (slight increase in myotonic tone) [3, 5, 6]. In severe course, a moderate decrease in all indicators (both active and passive mechanisms of regulation of microcirculation) was observed. In cirrhosis of the liver there is a slight increase in all parameters except  $A_{\max}N$ , in cirrhosis of the liver the system (L-arginine-NO) of the reticulo-endothelial system of the liver is depleted, which causes deterioration of microcirculation [10, 16, 19].

In general, the hepatic impairment was the highest in liver cirrhosis in most cases. This is due to hyperproduction and/or delayed utilization of vasoconstrictors, as well as structural and functional alteration of the liver with liver cirrhosis, which is in line with the literature [1, 3, 8].

The correlation analysis revealed a significant relationship between the values of many wavelet analysis and endothelial function (table 6).

**Table 6. In the study of correlating relationships between the values of endothelial function and laser Doppler flowmetry, differences were found depending on the contingent of the examined**

IHD (n = 30)	IHD + DLD (n = 25)	DLD (n = 102)
Direct correlation	Direct correlation	Direct correlation
Between $A_{\max}$ E and EDVD $r = (0.48)$ , $P < 0.05$	Between $A_{\max}$ E and IM $r = (0.82)$ , $P < 0.05$	Between $A_{\max}$ C and EDVD $r = (0.42)$ , $P < 0.05$
Between $A_{\max}$ E and EIDV $r = (0.47)$ , $P < 0.05$ ;	Between $A_{\max}$ E and EIVD $r = (0.53)$ , $P < 0.05$	Inverse correlation dependence
Between $A_{\max}$ N and IM $r = (0.54)$ , $P < 0.05$	Between $A_{\max}$ M and Wf $r = (0.53)$ , $P < 0.05$	Between $A_{\max}$ E and EIVD $r = (-0.43)$ , $P < 0.05$
Between $A_{\max}$ M and Wf $r = (0.44)$ , $P < 0.05$	Between $A_{\max}$ M and IM $r = (0.43)$ , $P < 0.05$	Between $A_{\max}$ M and EIVD $r = (-0.60)$ , $P < 0.05$
Between $A_{\max}$ C i EDVD $r = (0.76)$ , $P < 0.05$	Between $A_{\max}$ C and Wf $r = (0.45)$ , $P < 0.05$	Between $A_{\max}$ R and EIVD $r = (-0.57)$ , $P < 0.05$
Between SI and EDVD $r = (0.56)$ , $P < 0.05$	Between SI and CEC $r = (0.41)$ , $P < 0.05$	Between SI and EDVD $r = (-0.73)$ , $P < 0.05$
	Between SI and CBF $r = (0.47)$ , $P < 0.05$	Between SI and EIDV $r = (-0.37)$ , $P < 0.05$
	Between SI and EDVD $r = (0.92)$ , $P < 0.05$	
	Between SI and EIDVD $r = (0.81)$ , $P < 0.05$	
	<i>Inverse correlation:</i>	
	Between $A_{\max}$ M and EDVD $r = (-0.45)$ , $P < 0.05$	
	Between $A_{\max}$ M and EIVD $r = (-0.67)$ , $P < 0.05$	
	Between $A_{\max}$ C and CEC $r = (-0.42)$ , $P < 0.05$	
	Between $A_{\max}$ C and IM $r = (-0.46)$ , $P < 0.05$	
	Between $A_{\max}$ C and EDVD $r = (-0.93)$ , $P < 0.05$	
	Between $A_{\max}$ C and EIVD $r = (-0.47)$ , $P < 0.05$	
	Between SI and Wf $r = (-0.57)$ , $P < 0.05$	
	Between SI and IM $r = (-0.45)$ , $P < 0.05$	

This indicates the presence of features of CHF formation in these groups, which is confirmed by the greater number of reliable correlations in the analysis of these patients with IHD and DLD in isolation, compared with patients with the combination of IHD and DLD.

In the study of microcirculation in patients with IHD, signs of spasm of the precapillary sphincters were noted, due to increased myotonus, decreased blood circulation of the microcirculation system, which is consistent with the results of other studies [16, 19]. This is due to the overproduction of endothelin, thromboxane A<sub>2</sub>, angiotensin II, and other pro-inflammatory cytokines with vasoconstrictive effects.

We found some differences depending on changes in the state of microcirculation from contractility of the left ventricle in patients with coronary heart disease, depending on the presence of concomitant DLD. In patients with isolated IHD as TFlv decreases, there are clear signs of decreased capillary blood flow, probably due to the deterioration of central hemodynamics, atherosclerotic changes in blood vessels, and an increase in their tone.

In patients with IHD and  $E_{Flv} < 40\%$  increase in vascular tone – was higher compared to patients with higher  $E_{Flv}$  values, which may be due to phase changes in the metabolism of vasoactive substances (proinflammatory cytokines: IL1, IL6, TNF- $\alpha$ , prostacyclin, interferon- $\gamma$  etc.) [2, 3, 7].

Comparison of LDF and wavelet analysis in patients with coronary artery disease with similar  $E_{Flv}$  shows marked differences in their values, especially with initial and severe HF.

Thus, at  $E_{Flv} > 40\%$  in patients with IHD in the presence of DLD, there are noticeable tendencies to a higher myotonic tone, a decrease in the activity of passive mechanisms of regulation of microcirculation, a lower level of microcirculation compared with patients without DLD, which may be due to some extent related to swelling of the Disse space, as well as star cell contraction. When  $E_{Flv} < 40\%$  among patients with IHD, the degree of decrease in the regulation of active and passive mechanisms of regulation of microcirculation is more pronounced in diastolic dysfunction type pseudonormalization or restrictive type ( $E/A > 1.0$ ), the nature of the changes characteristic of the smoothed plateau type curve.

In patients with coronary artery disease in the presence of DLD at  $T_{Flv} > 40\%$ , there is a decrease in the level of microcirculation by increasing the neuro- and myotonus, possibly due to the depletion of the production of vasoactive substances. In patients with coronary artery disease with  $E_{Flv} < 40\%$  with concomitant DLD there is an increase in the influence of active mechanisms of regulation of microcirculation (by indicators  $A_{max}E$ ,  $A_{max}N$ ,  $A_{max}M$ ), while reducing the impact of passive.

This is probably explained by the violation of the disposal of vasoactive substances, due to irreversible morphofunctional changes in the liver at the stage of decompensation of HF, as well as pronounced fibrosis and the formation of regeneration nodes, which disrupt the cytoarchitectonics of the liver and, as a consequence, the morphology of deceleration of blood stream in the microcirculatory bed due to stagnation, inflammation, metabolic acidosis.

In patients with coronary heart disease without DLD, lower values of  $A_{max}E$ ,  $A_{max}H$ , and  $A_{max}M$  were observed, indicating a more pronounced increase in neurotonus, myotonus, impaired release of nitric oxide, as opposed to microcirculation in patients with concomitant DLD.

In patients with DLD there is a marked decrease in blood flow of the microcirculatory bed, as well as a significant disturbance of venous outflow. In this case, we detected phase changes in LDF indices in DLD of different severity: with DLD of moderate severity, venous outflow disturbance is more pronounced, neurotonus and myotonus of precapillary sphincters are more reduced compared with patients with both mild and severe liver lesions.. This can be explained by the hyperactivity of the L-arginine-NO system in patients with moderate severity of hepatitis, and in severe hepatitis and, in particular, in liver cirrhosis, the L-arginine-NO system of the reticulo-endothelial system of the liver is depleted, causing blood flow to deteriorate [3, 4, 7, 8, 19].

**Conclusions.** In our work optimization of diagnostics of hemodynamic disorders in patients with IHD is presented, depending on the presence of concomitant DLD. It is shown that concomitant DLD in patients with coronary heart disease significantly affect the systolic and diastolic functions of the LV and the dependence of changes in microcirculation on the development of CHF, which should be taken into account when evaluating the results of the examination and clarifying the effectiveness of treatment of such patients.

1. In patients with coronary artery disease with the deterioration of the contractile capacity of the LV and its diastolic filling, there is a progression of disorders of microcirculation. Among patients with  $E_{Flv} > 40\%$  at  $E/A < 1.0$   $A_{max}R$  was

- higher compared to patients with preserved diastolic LV function. In patients with pseudonormal and restrictive types, inhibition of regulation of active and passive mechanisms of regulation of microcirculation is noted.
2. Among patients with IHD in the presence of concomitant DLD at  $EFlv > 40\%$  lower values of  $A_{max}R$  and  $A_{max}C$  are noted, which indicates less influence of passive mechanisms of regulation of microcirculation; however, in  $EFlv < 40\%$ , such patients showed a marked decrease in  $A_{max}R$  and  $A_{max}C$  with an increase in  $A_{max}E$ , compared with patients without concomitant DLD.
  3. In patients with DLD, compared to healthy wavelet analysis, there were phase changes in  $A_{max}E$ ,  $A_{max}M$ ,  $A_{max}N$ ,  $A_{max}R$  and IS depending on the severity of liver damage.

**Conflict of interests.** Authors declare no competing interests.

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**ОСОБЛИВОСТІ МІКРОЦИРКУЛЯТОРНОЇ ДИСФУНКЦІЇ  
ЗА ПОКАЗНИКАМИ ВЕЙВЛЕТ-АНАЛІЗУ ЛАЗЕРНОЇ ДОППЛЕРІВСЬКОЇ  
ФЛОУМЕТРІЇ У ХВОРИХ НА ШЕМІЧНУ ХВОРОБУ СЕРЦЯ ТА СУПУТНИМИ  
ДИФУЗНИМИ ЗАХВОРЮВАННЯМИ ПЕЧІНКИ**

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**Мета.** Визначити особливості розвитку порушень мікроциркуляції за даними вейвлет-аналізу лазерної доплерівської флоуметрії (ЛДФ) у хворих на ішемічну хворобу серця (ІХС) залежно від наявності супутніх дифузних захворювань печінки. **Матеріали і методи.** Обстежено 187 осіб, середній вік –  $(46,1 \pm 17,4)$  року. І групу становили 55 хворих на ІХС з СН I–II Б стадії, I – IV ФК, середній вік  $(61,5 \pm 12,8)$  року, з них 16 жінок (29 %), фракція викиду лівого шлуночка (ЛШ) –  $(44,2 \pm 8,6)$  %. Середня тривалість ІХС становила  $(8,2 \pm 5,7)$  року. І група розподілена на підгрупи А і Б залежно від відсутності (ІА) чи наявності (ІБ) у хворих супутніх дифузних захворювань печінки (ДЗП). У II групі (група порівняння) обстежено 102 хворих на ІХЗ і ДЗП, середній вік  $(37,3 \pm 15,2)$  року. До III (контрольну) групи увійшло 35 практично здорових, середній вік  $(32,4 \pm 7,4)$  року. Результати обстеження хворих II групи додатково проаналізувано залежно від тяжкості проявів ураження печінки: ПА – 48 хворих з мінімальним синдромом цитолізу і холестазу (збільшення вмісту АлАТ менше ніж в 5 разів, білірубін – менше 100 мкмоль/л); ПБ – 42 хворих з помірним синдромом цитолізу та холестазу (збільшення вмісту АлАТ в 5–10 разів, білірубін – від 100 до 200 мкмоль/л); ПВ – 12 хворих на цироз печінки. ЛДФ здійснювали за допомогою

лазерного доплерівського флоуметра ЛАКК-02 (НПП «Лазма», РФ) за загальноприйнятою методикою. Також проводили аналіз показників Вейвлет перетворення ЛДФ-кривих, що графічно відображає залежність амплітуд цих видів коливань від їх частот. **Висновки.** В хворих на ІХС із зниженою систолічною функцією ЛШ та погіршеним діастолічним наповненням виявлено прогресуючу мікроциркуляторну дисфункцію. У дослідженні було доведено, що наявність при ІХС супутніх ДЗП викликали порушення регуляції системи мікроциркуляції. При ДЗП виявлено фазний характер змін показників регуляції системи мікроциркуляції залежно від тяжкості перебігу ураження печінки. Нами показано цінність вейвлет-аналізу ЛДФ в дослідженні мікроциркуляторних змін для виявлення стадій порушення регуляції системи мікроциркуляції та їх наявності неінвазивним шляхом у хворих на ІХС з супутніми ДЗП.

**Ключові слова:** ішемічна хвороба серця; лазерна доплерівська флоуметрія; вейвлет-аналіз; дифузні захворювання печінки.

ОСОБЕННОСТИ МИКРОЦИРКУЛЯТОРНОЙ ДИСФУНКЦИИ  
ПО ДАННЫМ ВЕЙВЛЕТ-АНАЛИЗА ЛАЗЕРНОЙ ДОППЛЕРОВСКОЙ  
ФЛОУМЕТРИИ У БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА  
И СОПУТСТВУЮЩИМИ ДИФУЗНЫМИ ЗАБОЛЕВАНИЯМИ ПЕЧЕНИ

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**Цель.** Изучить особенности развития нарушений микроциркуляции по данным вейвлет-анализа лазерной доплеровской флоуметрии (ЛДФ) у больных ишемической болезнью сердца (ИБС) в зависимости от наличия сопутствующих диффузных заболеваний печени (ДЗП). **Материалы и методы.** Обследовано 187 человек, из них 34 женщины и 154 мужчин, средний возраст –  $(46,1 \pm 17,4)$  года. I группа – 55 больных ИБС с СН I–II Б стадии, I–IV ФК, средний возраст  $(61,5 \pm 12,8)$  года, фракция выброса левого желудочка – ЛЖ  $(44,2 \pm 8,6)$  %. I группа разделена на подгруппы А и Б в зависимости от отсутствия (IA) или наличия (IB) у больных ИБС сопутствующих ДЗП. Во II группу (группа сравнения) вошло 102 больных ДЗП, средний возраст  $(37,3 \pm 15,2)$  года. III (контрольную) группу составили 35 практически здоровых, средний возраст  $(32,4 \pm 7,4)$  года. Результаты обследования больных II группы дополнительно подразделены в зависимости от тяжести поражения печени на подгруппы: ПА – 48 больных с минимальным синдромом цитолиза и холестаза (увеличение содержания АлАТ менее чем в 5 раз, билирубин – менее 100 мкмоль/л); ПБ – 42 больных с умеренным синдромом цитолиза и холестаза (увеличение содержания АлАТ в 5–10 раз, билирубин – от 100 до 200 мкмоль/л); ПВ – 12 больных с циррозом печени. ЛДФ проводили с помощью лазерного доплеровского флоуметра ЛАКК-02 (НПП «Лазма», РФ) по общепринятой методике. Также проводили анализ показателей вейвлет-преобразования ЛДФ-кривых, графически отображающих зависимость амплитуды этих видов колебаний от их частоты. **Выводы.** У больные ИБС со сниженной систолической функцией ЛЖ и нарушенным диастолическим наполнением отмечалась прогрессирующая микроциркуляторная дисфункция. Наличие при ИБС сопутствующих ДЗП вызывало нарушение регуляции системы микроциркуляции. При ДЗП обнаружен фазный характер изменений показателей регуляции системы микроциркуляции в зависимости от степени тяжести течения поражения печени. В работе показана роль вейвлет-анализа ЛДФ в исследовании микроциркуляторной дисфункции для выявления стадий нарушений регуляции системы микроциркуляции неинвазивным путём у больных ИБС с сопутствующими ДЗП.

**Ключевые слова:** ишемическая болезнь сердца; лазерная доплеревская флоуметрия; вейвлет-анализ; диффузные заболевания печени.