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ANALYSIS OF DIFFERENCES IN LABORATORY PARAMETERS IN PATIENTS WITH SILICOSIS DEPENDING ON THE LEVEL OF LEFT VENTRICULAR EJECTION FRACTION

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АНАЛИЗ РАЗЛИЧИЙ В ЛАБОРАТОРНЫХ ПОКАЗАТЕЛЯХ У ПАЦИЕНТОВ С СИЛИКОЗОМ В ЗАВИСИМОСТИ ОТ УРОВНЯ ФРАКЦИИ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА

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SILIKOZ BILAN OG‘RIGAN BEMORLARDA CHAP QORINCHA TEBRANISH FRAKSIYASI DARAJASIGA QARAB LABORATORIYA KO‘RSATKICHLARIDAGI FARQLARNI TAHLIL QILISH

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Цель: *повышение качества ранней диагностики сердечно-сосудистой патологии у пациентов с силикозом на основе изучения роли цитокинов и гемодинамических нарушений в развитии фиброза и эндотелиальной дисфункции.* ***Материал и методы:*** *все 146 человек, включенных в исследование (126 – основная группа и 20 здоровых добровольцев), прошли эхокардиографию на ультразвуковом аппарате, оснащенном секторным датчиком с частотой 4,5-7 мГц. Исследование проводилось утром, в положении пациента лежа на левом боку и на спине. За день до и в день исследования участникам рекомендовалось избегать интенсивных физических нагрузок и обильной пищи.* ***Результаты:*** *проведенный корреляционный анализ позволил выявить зависимость между фракцией выброса левого желудочка и рядом патогенетических маркеров силикоза, включая показатели системного воспаления (активность миелопероксидазы, эластазы нейтрофилов, концентрации TNF-α, интерлейкина-8) и маркеры эндотелиальной дисфункции (концентрация эндотелина-1).* ***Выводы:*** *необходимо разработать инновационные подходы к лечению и профилактике для предотвращения серьезных долгосрочных сердечно-сосудистых осложнений у лиц, подверженных профессиональному риску.*

Ключевые слова: *силикоз, эхокардиография, эндотелин-1, ФНО-α, диастолическая дисфункция, фракция выброса.*

Maqsad: *silikozli bemorlarda yurak-qon tomir patologiyasini erta tashxislash sifatini yaxshilash, fibroz va endotelial disfunktsiya rivojlanishida sitokinlar va gemodinamik kasalliklarning rolini o’rganish.* ***Material va usullar:*** *tadqiqotga kiritilgan barcha 146 kishi (asosiy guruhda 126 va 20 sog’lom ko’ngilli) 4,5-7 MGts chastotali sektor transduseri bilan jihozlangan ultratovush apparati yordamida ekokardiografiyadan o’tkazildi. Tekshiruv ertalab, bemor chap tomonida va chalqancha yotgan holda o’tkazildi. Tadqiqotdan bir kun oldin va tadqiqot kuni ishtirokchilarga intensiv jismoniy faollik va og’ir ovqatlardan saqlanish tavsiya qilindi.* ***Natijalar:*** *o’tkazilgan korrelyatsiya tahlili chap qorincha fraksiyasi va silikozning bir qator patogenetik markerlari, jumladan, tizimli yallig’lanish ko’rsatkichlari (miyeloperoksidaza, neytrofil elastaza faolligi, TNF-α, interleykin-8 konsentratsiyasi) va endotelial disfunktsiya markerlari (endotelin-1 konsentratsiyasi) o’rtasidagi bog’liqlikni aniqladi.* ***Xulosalar:*** *kasbiy xavf ostida bo’lgan shaxslarda jiddiy uzoq muddatli yurak-qon tomir asoratlarining oldini olish uchun davolash va oldini olishga innovatsion yondashuvlar zarur.*

Kalit so’zlar: *silikoz, ehokardiyografiya, endotelin-1, TNF-α, diastolik disfunktsiya, tebranish fraktsiyasi.*

Occupational morbidity in the mining industry continues to be one of the highest on average in the country. Its prevention and reduction is one of the most important tasks facing the leadership of the mining industry and the healthcare system of the Republic of Uzbekistan [11].

Cardiovascular diseases (CVD), the most common of which are arterial hypertension and coronary heart disease, occupy the main place in the structure of mortality and disability of the working population [1-3,5,7]. A large number of population-based studies of blood pressure levels have been accumulated in various countries and regions. The causes leading to increased incidence of hypertension and associated diseases are diverse [4,10]. Therefore, they should be specifically assessed in relation to different regions, ethnic groups, professions, in order to develop the most effective methods of dealing with them. Thus, a high prevalence of the disease among those working in hazardous working conditions, in particular miners, has been shown (Bondarev O.I., Bugaeva M.S., 2015).

Severe and specific working conditions in the coal mining industry are determined by microclimatic conditions directly at the workplace, dustiness, air pollution of the working area, high noise levels, vibration, severity and intensity of work, length of service, etc [9]. All this, along with traditional risk factors for the development of CVD (smoking, genetic factors, metabolic disorders and environmental unfavorable factors, etc.) contribute to the high prevalence of hypertension among coal mine workers [6,8]. The prognosis of patients with AH is determined not only by the degree of increase in blood pressure (BP), but also, first of all, by the presence of initial changes in the vessels of the lungs, which are trigger mechanisms for triggering the main pathological processes, including further myocardial hypertrophy - a clinically substantiated condition for cardiovascular complications (Yakovlev Yu.V. et al., 2018).

The question of finding the best ways to predict the development of diseases of the circulatory system, taking into account the influence of harmful production factors in the development of prognostic methods, remains open.

Purpose of the study

Improving the quality of early diagnosis of cardiovascular pathology in patients with silicosis based on the study of the role of cytokines and hemodynamic disorders in the development of fibrosis and endothelial dysfunction.

Material and methods

All 146 persons included in the study (126 representatives of the main group and 20 healthy volunteers) underwent echocardiography (EchoCG) on an ultrasound machine equipped with a sector transducer with a frequency of 4.5-7 MHz. Standard echocardiographic positions were used. The study was conducted in the morning, lying on the left side and on the back. The day before and on the day of the study, participants it was recommended to avoid severe physical exertion and heavy meals. The following indicators were registered:

- diameter of the ascending aorta - in the left parasternal position along the long axis of the left ventricle (LV), in M-scanning mode, from the inner contour of the anterior wall of the aorta to the inner contour of the lower wall, in the region of the maximum diameter of the aortic bulb;

- diameter of the left atrium - in the left parasternal position along the LV long axis, in M-scan mode, perpendicular to the LV axis, from the inner contour of the anterior to the inner contour of the inferior LV wall;

- end diastolic and systolic LV sizes (LV EDD and LV ESD, respectively) - in the left parasternal position along the long axis of the left ventricle, in the M-mode at the level of the basal segment of the LV cavity perpendicular to the long axis of the ventricle, from the inner surface of the myocardium of the interventricular septum (IVS) to the inner surface of the myocardium (that is, excluding the endocardium) of the posterior wall of the left ventricle (ZSLZh) in diastole and systole, respectively, with the determination of the phase of the cardiac cycle according to the synchronous electrocardiographic curve;

- LV end-diastolic volume (LV EDV) was calculated using the Teichholtz formula using the LV EDD determined as described above;

- LV ejection fraction (LV EF) - was calculated as the ratio of the difference between LV EDV and LV final systolic volume to LV EDV, calculated as described above, expressed as a percentage;

- diastolic IVS thickness - was determined in the left parasternal position along the LV long axis, in M-mode, perpendicular to the long axis of the ventricle, at the level of the LV basal segment, at the end of diastole, from the endocardium-myocardium border from the LV side to inner border of the pericardium;

- the end diastolic size of the right ventricle (RV) was determined in the left parasternal position along the LV long axis, in M-mode, perpendicular to the long axis of the left ventricle, at the level of the LV basal segment, at the end of diastole, from the border of the endocardium-myocardium of the IVS from the side of the RV to internal contour of the anterior wall of the pancreas.

Dopplerography was performed for transpulmonary flow in the left parasternal position along the short axis of the left ventricle at the level of the aortic valve. The maximum blood flow velocity was recorded using pulsed wave Doppler mode. For the remaining valves, dopplerography was used in the apical position with visualization of the valves in 4, 5 and 2 chamber projections. To determine the maximum systolic flow rate through the aortic valve, both pulsed wave and continuous wave Doppler were used, for atrioventricular valves (mitral - MV and tricuspid - TK) - pulsed wave Doppler with registration of the maximum speeds of early and atrial diastolic filling.

The diastolic function of the ventricular myocardium was assessed by the ratio of the rates of early and atrial diastolic filling of the ventricles (E/A). To determine the type of diastolic dysfunction, the Canadian classification of diastolic function was used: with a ratio of maximum speeds of 1-2, normal diastolic function or diastolic dysfunction (LVDD) type 2 (pseudonormalization) was diagnosed in case of pronounced signs of myocardial dysfunction, with a ratio of less than 1, LVDD type 1 was diagnosed (slow down relaxation), with a ratio of more than 2 - LVDD type 3 (restriction). In the course of the study, the frequency response of groups was determined according to various options for diastolic function.

Statistical processing. All data obtained as a result of echocardiography were entered into Excell summary tables with the distribution of study participants by clinical groups. In each group, the following were calculated: the arithmetic mean and its standard error for parametric values obeying a normal distribution, and the frequency of occurrence of features for nonparametric values.

Intergroup comparison in the case of parametric values was carried out using unpaired Student's t-test with Bonferroni correction for multiple comparisons (because the study included 4 clinical groups) and using tabular chi-square test in the case of frequency comparison and assessment of its reliability according to tables depending on the number degrees of freedom. Differences were considered significant if the probability of the null hypothesis was less than 0.05 (less than 5%).

Results of the study

In patients with stage 1 and stage 2 silicosis, the heart rate significantly exceeds the heart rate in the CG ($p<0.001$ significance of the difference with the stage 1 silicosis group and $p<0.05$ with the stage 2 silicosis group) (table 1). An echocardiographic study found that in all clinical subgroups of the main study group, the diameter of the ascending aorta significantly exceeded the diameter recorded in the CG ($p<0.001$ with silicosis groups of stages 1 and 2, $p<0.01$ with groups of silicosis of stage 3), and in patients Stage 1 ascending aortic diameter was significantly smaller in more advanced stage patients ($p<0.05$ with stage 2 patients), although significance between stage 1 and stage 3 patients was not achieved, this is probably due to the small number of patients with stage 3 silicosis. The LA diameter also increased with the progression of the disease, while statistical significance with CG was achieved only in patients with stage 3 silicosis ($p<0.05$).

Left ventricular systolic function was reduced in patients with stage 3 silicosis (52%) relative to the reference norm (55%) and relative to CG and patients with stage 2 and 1 silicosis (52%), but without reaching the level of significance. Since the main criterion for cardio toxicity is considered to be a decrease in LV EF, in the present study, patients with LV EF below the reference norm of 55% were identified. There were 4 such patients

and they all suffered from stage 3 silicosis. Regional dyskinesia was found in 3 patients with stage 3 silicosis (42.86%), in 5 patients with stage 2 silicosis (13.51%), and in none of the CG and stage 1 silicosis patients (chi square = 29.41 , p<0.001).

The diameter of the pancreas is increased in all groups of patients with silicosis relative to CG (p<0.001 in patients with stages 1 and 2 and p<0.01 in patients with stage 3), regardless of the stage of the disease.

Assessment of diastolic function showed that the number of patients with LV diastolic dysfunction increases with the increase in the stage: thus, in the CG in all patients, the diastolic function of both ventricles was normal, while 28.05% of patients with stage 1 silicosis 28 05% demonstrated the presence of LVDD1, and among patients with stages 2 and 3, LVDD1 was registered in 59.46% and 100%, respectively (chi square = 33.24, p<0.001). For the pancreas, the frequency of LVDD was 13.41%, 43.24% and 57.14%, respectively (chi square=24.50, p<0.001). A manifestation of diastolic dysfunction was a progressive decrease in the rate of early diastolic filling (significance of difference for the transmitral flow between patients with stage 2 silicosis and CG and patients with stage 1 silicosis - p<0.05 and for transtricuspid flow between patients with stage 2 silicosis and CG p<0.05 and patients with stage 1 silicosis - p<0.001) and an increase in atrial filling flow rate (significance of difference for the transmitral flow between patients with stage 1 silicosis and CG – p<0.05 and for transtricupid flow between patients with stage 3 silicosis and CG – p<0.01) (Table 1).

Table 1

Comparative characteristics of laboratory markers of systemic inflammation, endothelial dysfunction, myocardial damage and lipid status in silicosis patients with low and preserved LVEF

Index	Patients with LVEF below 55% (n=18) Patients with LVEF 55% and above (n=108) median		
MPO	14,06±0,46	4,87±0,33***	5,1
Neutrophil elastase	54,83±1,82	21,39±1,26***	20,95
Endothelin-1	109,22±2,95	49,78±2,60***	55,65
TNF-α	11,79±0,37	6,46±0,23***	7,05
Interleukin-8	31,45±1,13	13,12±0,75***	14,55
Wow	6,61±0,14	5,44±0,10***	5,55
Tr	2,58±0,13	2,02±0,06***	1,9
HDL-C 1	1,34±0,00	1,37±0,00***	1,35
LDL-C	4,85±0,05	4,33±0,06***	4,6
VLDL-C	1,13±0,06	0,88±0,03***	0,8
AT	4,87±0,11	3,97±0,08***	4,1
SK-MV	27,94±0,87	24,11±0,56***	25
Age, years	54,67±1,62	47,29±0,55***	48
Heart rate, beats per minute	75,44±1,05	81,08±1,40**	75
Aorta, mm	31,94±0,50	31,01±0,31	30
left atrium, mm	35,78±0,65	30,53±0,17***	30
KDR LV, mm	57,11±1,07	47,38±0,37***	49
KSR LV, mm	44,72±1,04	29,93±0,31***	31
LV EDV, ml	163,39±7,18	104,99±1,84***	114
LV EF, %	44,17±0,94	66,30±0,48***	66
MZHP, mm	10,39±0,41	10,94±0,10	11
ZSLZh, mm	10,06±0,17	10,59±0,11*	10
Right ventricle, mm	27,22±0,81	28,89±0,19	29
Ao, m/s	117,22±5,22	128,82±1,44*	130
CLLA, m/s	80,83±2,83	91,06±1,00**	91
E MK, m/s	72,94±3,39	75,74±2,35	73
A MK, m/s	86,50±6,24	71,65±1,42*	69
E TC, m/s	43,44±2,51	62,15±1,72***	59,5
A TK, м/s	51,39±0,41	47,15±0,96***	48

Note. * – Reliability of intergroup differences. One sign – p<0.05, two signs – p<0.01, three signs – p<0.001.

The next step in the hemodynamic branch of the study was to determine the prognostic factors for the development of systolic myocardial dysfunction. For this purpose, the information content of all studied pathogenetic markers, which significantly differ in patients with low and intact LV EF, was studied. Reduced LV EF is observed only in patients with stage 3 silicosis. The absolute risk of developing LV systolic dysfunction in patients with stage 3 silicosis is 66.67%. Thus, the presence of a patient with stage 3 silicosis can be considered one of the prognostic markers for the development of LV systolic dysfunction, the sensitivity of which is 100%, specificity - 91.74%%, information content - 93.65% (p<0.001).

For all laboratory markers, the diagnostic significance and RR for the formation of low LV EF were calculated. As can be seen from the presented data, the diagnostic value of individual markers was in the range of 64.29% -73.02%. An attempt to use a combination of markers did not increase the informativity of the study compared to individual tests (68.25%). Thus, the present study showed that the patient's belonging to the 3rd stage of silicosis had the greatest prognostic value (Table 2).

Table 2

Prognostic significance of various markers in terms of a decrease in the systolic function of the LV myocardium

Forecast marker	Individuals with an LVEF below 55% Individuals with an LVEF of 55% or more				Chi square	OP	Informative		
	Number of persons with recognition	Abs. risk	Number of persons with recognition	Abs. risk			Sensitivity	Specificity	Diagnostic value
Silicosis stage 3	18	66,67	9	0,00	23,80***		100,00	91,74	93,65
MPO	18	28,57	45	0,00	21,06***		100,00	58,72	65,08
Neutrophil elastase	18	28,57	45	0,00	21,06***		100,00	58,72	65,08
Endothelin-1	18	28,57	45	0,00	21,06***		100,00	58,72	65,08
TNF-α	18	28,57	45	0,00	21,06***		100,00	58,72	65,08
Interleukin-8	18	28,57	45	0,00	21,06***		100,00	58,72	65,08
Wow	17	26,98	46	1,59	16,66***	17,00	94,44	57,80	64,29
Tr	16	27,59	42	2,94	15,48***	9,38	88,89	61,47	67,46
HDL-C 1	12	25,53	35	7,59	7,55**	3,36	66,67	67,89	73,02
LDL-C	15	30,00	35	3,95	16,47***	7,60	83,33	67,89	73,02
VLDL-C	16	27,59	42	2,94	15,48***	9,38	88,89	61,47	67,46
AT	17	28,81	42	1,49	19,09***	19,31	94,44	61,47	67,46
SK-MV	14	23,33	46	6,06	7,67**	3,85	77,78	57,80	64,29
age	14	23,73	45	5,97	8,09**	3,97	77,78	58,72	65,08
Sum of points, except for stage 3 silicosis	18	30,51	41	0,00	23,80***		100,00	62,39	68,25

Note. * – The reliability of the frequency difference in the occurrence of the sign, depending on the LV EF. Three signs - p<0.001.

Atherogenic dyslipidemia acts as one of the key mechanisms leading to disruption of the structure and functions of the endothelium. In the framework of this study, it was found that an increase in the levels of atherogenic lipids (total cholesterol, triglycerides, VLDL) and the coefficient of atherogenicity shows only a weak correlation with a decrease in the left ventricular ejection fraction (LVEF) (p<0,01). This observation is consistent with the previously identified dependence, where the activity of systemic inflammation and the degree of endothelial dysfunction directly affect the LVEF value. In addition, a statistically significant but very weak negative relationship was found between LVEF and the concentration of LDL-C, as well as CK-MB (p<0.05). On the contrary, there was a very weak positive correlation with the level of antiatherogenic HDL-C (p<0.05).

Correlation analysis has established that the left ventricular ejection fraction (LVEF) is inversely proportional to its systolic and diastolic dimensions (LV EDR, TFR and EDV). It was also found that LVEF is weakly negatively associated with the size of the aortic root and left atrium, as well as with heart rate. An average negative correlation was observed between LVEF and the peak filling rate of the left and right atria (p<0.01). At the same time, the wall thickness of the left ventricle, the size of the right ventricle, and the peak rate of early diastolic filling of the left ventricle.

Conclusions

1. The results of the study demonstrate an inverse relationship between the systolic function of the left ventricle and the severity of systemic inflammation, endo-

thelial dysfunction, dilation of the left chambers and impaired diastolic function of the myocardium.

2. It is necessary to develop innovative approaches to treatment and prevention in order to prevent serious long-term cardiovascular complications in people at occupational risk.

3. To reduce the likelihood of occupational diseases in the mining and metallurgical industries, it is necessary to introduce modern technologies and improve sanitary and hygienic conditions, as well as provide high-quality medical care, including early detection, rehabilitation and secondary prevention.

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ANALYSIS OF DIFFERENCES IN LABORATORY PARAMETERS IN PATIENTS WITH SILICOSIS DEPENDING ON THE LEVEL OF LEFT VENTRICULAR EJECTION FRACTION

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Objective: *To improve the quality of early diagnosis of cardiovascular pathology in patients with silicosis by studying the role of cytokines and hemodynamic disorders in the development of fibrosis and endothelial dysfunction.* ***Material and methods:*** *All 146 people included in the study (126 in the main group and 20 healthy volunteers) underwent echocardiography using an ultrasound machine equipped with a sector transducer with a frequency of 4.5-7 MHz. The examination was performed in the morning, with the patient lying on his left side and on his back. The day before and on the day of the study, participants were advised to avoid intense physical activity and heavy meals.* ***Results:*** *The conducted correlation analysis revealed a relationship between the left ventricular ejection fraction and a number of pathogenetic markers of silicosis, including systemic inflammation indicators (activity of myeloperoxidase, neutrophil elastase, TNF-α, interleukin-8 concentrations) and markers of endothelial dysfunction (endothelin-1 concentration).* ***Conclusions:*** *Innovative approaches to treatment and prevention are needed to prevent serious long-term cardiovascular complications in individuals at occupational risk.*

Key words: *silicosis, echocardiography, endothelin-1, TNF-a, diastolic dysfunction, ejection fraction.*

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