PSYCHOLOGY AND EDUCATION (2021) ISSN: 0033-3077 Volume: 58(4): Pages: 1265 - 1276
Article Received: 08th October, 2020; Article Revised: 15th February, 2021; Article Accepted: 20th March, 2021

Evaluation of the Relationship between Cardiac and Renal Fibrosis Markers in Different Hemodynamic Types of Chronic Heart Failure with and Without Anemia

Gadaev Abdigaffar Gadaevich[1]
Khalilova Feruza Abdujalolovna [2]
Akhmedov Khalmurad Sadullayevich[3]
Tashkent Medical Academy and Bukhara Medical Institute,Uzbekistan

Abstract. Renal fibrosis markers were evaluated in dynamics to study specific changes in the kidneys of patients with different hemodynamic types and functional classes of chronic heart failure with anemia and to evaluate the effectiveness of complex treatment. The renal fibrosis marker TGF-β1 in the blood was 2591.0 ± 108.4 and 755.0 ± 18.87 pg / ml, respectively, in chronic heart failure with anemia and without anemia ($p<0.01$). This was indicative of a fibrosis process occurring in the kidney. After complex treatments with the addition of iron, the TGF-β1 index decreased by 2.25 times (p ,0.01), the clinical condition, quality of life and resistance to physical exertion changed significantly positively.

Keywords:chronic heart failure, chronic kidney disease, renal dysfunction, fibrosis markers, cystatin-C, TGF-β1, ferrokinetic indicators, galectin-3, hemodynamic types.

Introduction.CHF is a disease that is among the leading causes of morbidity and mortality in the world and has significant social and economic significance. Despite advances in the treatment of cardiovascular disease over the past 20 years, this serious complication remains an unresolved clinical problem. According to the epidemiological survey, the prevalence of CHF in the U.S. and European countries ranged from 0.4% to 2%, a significant increase with age, reaching 10% in those over 60 years of age.

At the same time, the incidence of syphilis on the planet has been steadily increasing, reaching a level comparable to that of the most dangerous infectious epidemics in terms of scale and speed of spread (1). About 5.8 million people in the United States and 23 million people worldwide are infected with CHF(7).

It is known that the development of systemic organ damage in CHF plays an important role in the remodeling of the left ventricle of the heart from its earliest period (16).

According to the recommendations of the European Society of Cardiologists (ESC 2016), from 2016, patients with CHF are divided into 3 groups, taking into account hemodynamic disorders. According to the indicators of the left ventricular hematopoietic fraction, its decreased (<40%), intermediate (40-49%) and preserved (≥50%) types are distinguished. The standard composition of pharmacological treatment gives a relatively positive result in patients with a decrease in blood drive fraction. In contrast, almost no positive effect is observed in standard pharmacological treatments, with the exception of nitrates in the CHF where the driving fraction is preserved. Therefore, the decompensation phase of the disease leads to negative consequences in almost all cases. Indeed, a number of authors have suggested that left ventricular diastolic filling disorders play a more important role in the pathogenesis of syphilis than systolic dysfunction, depending on the severity of the disease and its consequences. The process of diagnosing diastolic CHF is complex and its pathophysiology has not been fully studied (12; 6; 3; 15; 10).

PSYCHOLOGY AND EDUCATION (2021) ISSN: 0033-3077 Volume: 58(4): Pages: 1265 - 1276
Article Received: 08th October, 2020; Article Revised: 15th February, 2021; Article Accepted: 20th March, 2021

As noted above, in addition to the prevalence of CHF, it is distinguished from a number of other diseases by its adverse effects and high disability rate [13]. The mean 5-year mortality rate in the population of patients with CHF (I-IV FC) was 59% in men and 45% in women, 6–7 times higher than in the general population of the same age (5; 8; 18; 37). Because the degree of damage to the myocardium, along with other organs and systems, ie comorbidity, is important in this complication, which determines the fate of patients and the consequences of the disease (15). Among them, anemia has a special place and in most cases is accompanied by CHF (11). Anemia not only exacerbates CHF symptoms, but also worsens quality of life by prolonging hospitalization, reduces endurance to physical exertion, and increases the risk of death by 2 or more times (14). It should be noted that there is a weak feedback between hemoglobin and the left ventricular blood drive fraction (28; 35).

A number of observations have shown that anemia is an independent risk factor in patients with CHF, in which myocardial oxygen supply is significantly reduced (17; 27).

It is known that in addition to anemia, a number of other polymorbid diseases are also detected in patients with CHF. Among them, renal dysfunction plays a leading role not only in the pathogenesis and development of CHF, but also in the development of anemia (26; 29). However, at the same time, such comorbid cases remain poorly understood from a scientific point of view. (36.)

The purpose of the study. Evaluation of the effectiveness of antianemic therapy based on standard therapy in renal and cardiac fibrosis processes in patients with different hemodynamic types of chronic heart failure (preserved intermediate and low) with anemia.

Material and methods. The 120 patients with CHF involved in the study were divided into 2 groups (75 of whom were anemic and 45 were anemic) and underwent excellent clinical and laboratory examinations. In order to carry out the tasks set before us, 75 patients with CHF anemia were divided into 3 groups (in each group there were 25 left ventricular hemorrhage fractions, intermediate and low ones). They ranged in age from 50 to 70 years and averaged 64.0 ± 5.0. All patients were followed up in an outpatient setting after treatment in a hospital setting. The clinical classification of the follow-up patients is given in Table 1.

Table 1
Classification of patients involved in the study

№	Indicators	I group n = 75		Group II n = 45	
		Absolutely	%	Absolutely	%
1.	Male	32	42,7	25	
2.	Female	43	57,3	20	55,5
3.	Ischemic heart disease	45	60.0	36	44,5
4.	Ischemic heart disease	25	33,4	8	17,8

	, post-infarction cardiosclerosis				
5.	Hypertension	5	6,6	1	2,2
6.	Obesity	12	16	11	24,5

Group I patients were given 200 mg of iron III hydroxide sucrose complex (venofer) intravenously as an antianemic treatment based on the standard treatment of CHF during hospital treatment. The total dose of the drug administered for the treatment of iron deficiency, using a special formula adopted for the treatment of venofer [total iron deficiency = body weight, kg x (150 - patient hemoglobin index Hb, g / l) x 0.24 + 500 mg] calculated.

Group II patients were prescribed the generally accepted CHF standard treatment.

Patients in both groups received angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists,--adrenoblockers, and mineralocorticoid receptor antagonists (as eplerenone-antifibrosis drugs) as standard treatment.

In the patients involved in the study, the diagnosis of CHF and its functional classes were determined on the basis of their complaints, anamnesis, objective examination and laboratory-instrumental examinations, as well as criteria of the New York Heart Association (New York Heart Association, 1964).

It was also based on the recommendation of the World Health Organization (hemoglobin <13.0 g / dl for men and <12.0 g / dl for women) as the primary criterion for anemia in group I patients.

Research results and discussion.Serum ferrokinetic parameters, cardiac and renal fibrosis markers, hemodynamic types, and the presence or absence of anemia were studied comparatively in all groups of patients involved in the study. Information about them is given in Table 2.

PSYCHOLOGY AND EDUCATION (2021) ISSN: 0033-3077 Volume: 58(4): Pages: 1265 - 1276
Article Received: 08th October, 2020; Article Revised: 15th February, 2021; Article Accepted: 20th March, 2021

Table 2

Indicators	Patients with chronic heart failure anemia and without anemia								
	Patients with left ventricular hemorrhage and anemia n = 25> 50%	Patients with left ventricular hemorrhage and n = 15> 50%	R	Patients with left ventricular hemorrhage fraction interstitial and anemia n=25 >40%=<50%	Patients with left ventricular hemorrhage fraction intermediate and incomplete n=15 >40%=<50%	R	Patients with decreased left ventricular hemorrhage fraction and anemia n=25 < 40%	Patients with decreased left ventricular hemorrhage and incontinence n=15 < 40%	R
Hemoglobin - g / l	98,5±1,2	139,9±2,0	<0,001	98,6±1,3	134,9±1,6	<0,001	98,5±1,2	139,9±2,0	<0,001
Iron - mk.mol / l	9,7±0,6	25,1±0,8	<0,001	9,4±0,8	22,7±0,6	<0,001	7,9±0,6	22,1±1,0	<0,001
Ferritin - mkg / l	202,3±14,9	332,5±30,5	<0,001	200,4±18,5	352,0±10,4	<0,001	101,0±3,3	363,0±15,9	<0,001
Transferin - g / l	3,92±0,24	4,3±0,3	<0,001	4,2±0,2	3,7±0,2	<0,05	4,8±0,3	3,6±0,37	<0,001
Galectin -ng / ml	22,54±1,1	19,23±1,12	<0,05	19,55±1,3	18,48±1,5	<0,05	19,02±1,17	13,37±1,4	<0,05
Aldesterone- pg / ml	566,7±14,3	526,6±13,8	<0,05	529,04±15,4	468,7±23,8	<0,05	485,2±14,4	406,3±20,3	<0,05
TGF-β1- pg / ml	2554,7±125,4	2209,4±122,2	<0,05	2832,7±176,0	2194,3±75,8	<0,05	2332,8±167,8	1994,2±73,1	<0,05
Cystatin C mg / l	1,39±0,05	1,25±0,05	<0,05	1,58±0,15	1,19±0,12	<0,05 1.32±0.12	1.32±0.12	1.26±0.02	<0,05
Ball filtration ml / min	65,6±2,45	68,4±2,3	<0,05	67,8±2,64	72,8±1,17	<0,05	58,2±1,7	69,95±1,05	<0,05
Sodium - m.mol / l	136,28±1,73	132,8±1,6	<0,05	138,24±1,72	141,2±1,2	<0,05	135,42±1,3	143,6±1,14	>0,05
Potassium- m.mol / l	7,86±0,5	7,9±0,5	<0,05	7,47±0,46	7,9±0,6	<0,05	7,5±0,5	7,9±0,62	<0,05
Chlorine ml.mol / l	104,1±1,56	103,4±1,5	<0,05	105,32±1,5	108,7±1,12	<0,05	106,2±1,45	109,7±1,13	<0,05

Different hemodynamic types of chronic heart failure are markers of cardiac and renal fibrosis and indicators of ball filtration rate in the absence of anemia and anemia.

In the groups where the left ventricular hemorrhage fraction was maintained and anemic, hemoglobin, iron, ferritin, and transferrin levels were found to be 29.6%, 61.3%, 39.1%, and 8.8% lower ($p < 0.001$), respectively, than in non-anemic groups. The left ventricular hemorrhage fraction was 26.9%, 55.8%, 43.1%, 13.5% in the intermediate group, and 29.5%, 64.2%, 72.1%, and 33.3% in the decreased hemorrhage fraction, respectively, with a reliable difference ($p < 0.001$). These indicators indicate that patients are reliably divided into groups based on hemoglobin indicators.

In recent years, galectin-3 has been proven to be a reliable marker of fibrosis in pathological processes in the body and primarily in the heart. However, although this marker has been studied in the CHF, there is no data in the available literature on its change in anemia. In the left ventricular hemorrhage fraction in which we observed, in the intermediate and decreased groups, when they were anemic and without anemia, the galectin-3 values were 22.5 ± 1.1 and 19.23 ± 1.1, 19.55 ± 1.3 and 18.5 ± 1.5, 19.02 ± 1.2, and 13.2 ± 1.4, respectively, in all cases. ng / ml was equal to ($p < 0.05$). At the same time, its indicators were 1.2, 1.1 and 1.4 times higher in different hemodynamic types, respectively, than in those without anemia.

It is known that aldosterone is actively involved not only in water-salt metabolism in the body, but also in fibrous processes, which has been proven in numerous studies. In recent years, there have been reports that this hormone is produced not only in the adrenal glands, but also in other internal organs, including the kidneys and heart. Numerous studies have been conducted on its modification under the influence of various FC and a number of drugs. However, data on aldosterone levels in the blood are insufficient when this severe complication occurs in comorbidity with anemia. In this context, we studied its efficacy in patients with CHF anemia and non-anemia.

At the same time, aldosterone was 1.1, 1.1, and 1.2 times ($p < 0.05$) higher reliably in patients with left ventricular hemorrhage, interstitial, decreased, and anemia, respectively, than in those without anemia. The indicators confirm that aldosterone in the blood increases not only due to the presence of hemodynamic types of CHF, but also the presence of anemia, and therefore the increase in fibrous processes.

TGF-$\beta_1$plays a leading role in the development of fibrous processes in the body and primarily in kidney tissue. However, there is insufficient data in scientific sources on the alteration of this cytokine when CHF passes with anemia. In patients with left ventricular hemorrhage fraction, intermediate, decreased, and anemia and anemia without follow-up, TGF-β_1 values were 2554.7 ± 125.4 and 2209.4 ± 122.2 ($p < 0.05$), 2832.7 ± 176.0, and 2194.3 ± 75.8 ($p < 0.05$), respectively. , 2332.8 ± 167.8 and 1994.2 ± 73.1 pg / ml ($p < 0.05$).

Cytokine levels were 13.5%, 22.5%, and 14.5%, respectively, in the presence of anemia and in the absence of anemia.

It is known that in recent years, special attention has been paid to cystatin-C in the assessment of renal function. It has a number of advantages over creatinine. Therefore, we determined cystatin-C levels in the

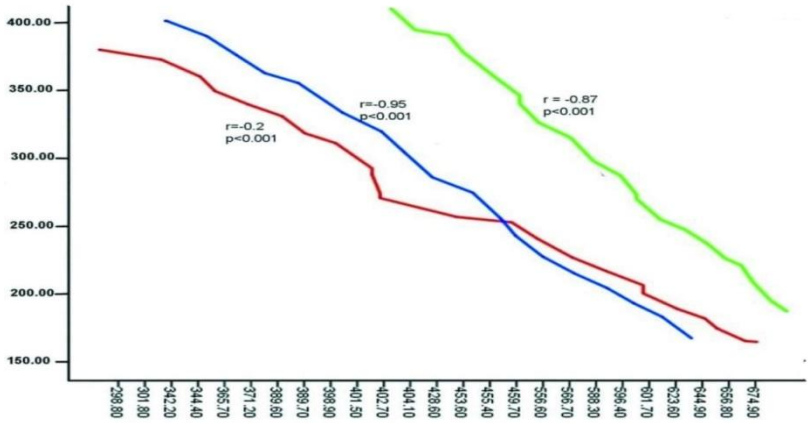
blood of patients in our follow-up and assessed glomerular filtration using it. Cystatin-C levels were 10.1%, 24.6%, and 4.54% higher, respectively, in patients with left ventricular hemorrhage fraction, interstitial, decreased, and anemic groups.

It has been shown that the early development of fibrous processes in the kidneys of patients with anemia and the process adversely affects the functional state of the kidneys.

Cystatin-C-derived globular filtration rates also confirmed these changes, i.e., when anemia was detected in all hemodynamic types, it was reliably reduced by 4.3%, 7.4%, and 20.2%, respectively, ($p < 0.05$) compared to non-anemia.

In the next phase of our study, the correlation between cardiac and renal fibrosis markers and fibrosis markers with the identified ferrokinetic parameters was studied. The relationship between the 6-minute walking test and aldosterone levels among all hemodynamic types of anemia with CHF is shown in Figure 1.

a six-minute walking test(M)



Aldasterone(pg/ml)

Green -Remained
Blue-Intermediate
Red-Decreased

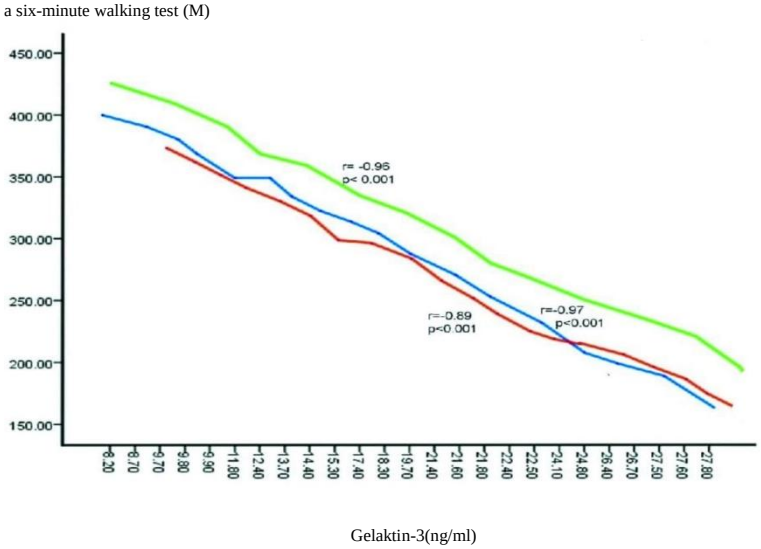
Indications of correlation between aldasterone and six-minute walking test in patients with left ventricular fibrillation fraction, intermediate and decreased in chronic heart failure with anemia

In which the left ventricular hemorrhage fraction was preserved, the correlation between the indicators recorded in intermediate and decreased patients was r = - 0.87, respectively; p <0.001, r = - 0.95; p <0.001 and r = - 0.2; p <0.01. In all cases, a reliable negative correlation was found between aldosterone and the 6-minute walking test. This confirms that an increase in aldosterone in the blood, which is one of the markers of fibrosis in the kidneys and heart, has a reliable negative effect on patients 'resistance to loads.

Also, the correlation between the 6-minute walking test and galectin-3, which is a reliable marker of fibrous processes in the heart, among all hemodynamic types of anemia, was r = - 0.95, respectively; p <0.001, r = -

0.97; p <0.001 and r = - 0.89; p <0.01 was equal to (Figure 2).

Figure 2



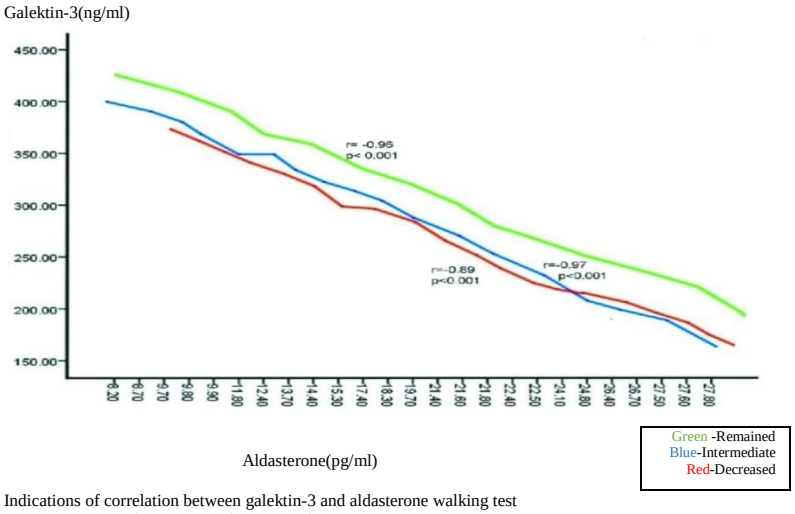
Indications of correlation between gelaktin-3 and six-minute walking test in patients with left ventricular fibrillation fraction, intermediate and decreased in chronic heart failure with anemia

This analysis showed a reliable inverse relationship between galectin-3 and all hemodynamic types and the 6-minute walking test.

Although the figures in Figures 1-2 above showed a reliable correlation between fibrosis markers and patient endurance in all types of CHF, but the high correlation CHF left ventricular hemorrhage fraction was preserved and was more pronounced in intermediate types (respectively r = - 0.87; p <0.001, r = - 0.95; p <0.001 and r = - 0.95; p <0.001, r = - 0.97; P <0.001). These results confirm the data in the literature on the fact that the diastolic type of CHF is accompanied by more fibrous processes.

In the next step, we studied the interaction between galectin-3 and aldesterone, which are reliable markers of fibrosis processes in the body (Figure 3).

Figure 3

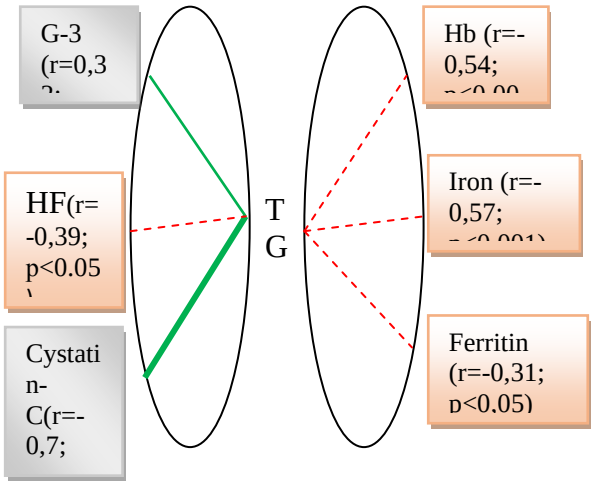


Indications of correlation between galektin-3 and aldasterone walking test in patients with left ventricular fibrillation fraction, intermediate and decreased in chronic heart failure with anemia

As shown in the diagram, these markers have a mutually reinforcing effect on each other, so an increase in one leads to an increase in the other. This process is confirmed by the existing positive correlation between them in all hemodynamic types of CHF, ($r = 0.94$; $p < 0.001$, $r = 0.95$; $p < 0.001$ and $r = 0.96$; $p < 0.001$, respectively). Consequently, when CHF is observed with anemia, fibrous processes in the body coexist and have a strengthening effect on each other.

Also, a reliable negative correlation was found between ferritin and fibrosis markers galectin-3 and aldosterone, which show iron reserves in the body in the group of anemia in which the CHF hemorrhage fraction was preserved ($r = -0.43$; $p < 0.05$ and $r = -0.42$; $p < 0.05$).

In the next stage, patients with CHF anemia and decreased left ventricular hemorrhage fraction were identified in the blood and with more TGF-β_1 reflecting tubulointerstitial processes in the kidney, ferrokinetic indicators and cardiac fibrosis marker galectin-3 and cystatin-C, widely used in recent years in the assessment of renal function we studied the dependencies (Figure 4).



HF - hemorrhage fraction

Figure 4

Correlation between TGF-β_1 and ferrokinetic parameters, galectin-3, cystatin-C, and hemorrhagic fraction in patients with decreased left ventricular hemorrhage fraction in chronic heart failure anemia

As shown in Figure 4, an increase in TGF-β_1 in the blood leads to a reliable decrease in the left ventricular hemorrhage fraction ($r = -0.39$; $p < 0.05$). It was also noted that TGF-β_1 was negatively correlated with ferrokinetic parameters. In this case, it corresponds to the hemoglobin index $r = -0.54$; $p < 0.001$, with serum iron $r = -0.57$; $p < 0.001$, with ferritin $r = -0.31$; $p < 0.05$ was detected. These indicators confirm that the renal fibrosis marker interacts with the markers confirming anemia, leading to the development of fibrous processes.

A study of ferrokinetic factors affecting ball filtration rate (BFR) revealed a number of correlations as shown in Figure 5. In particular, an increase in hemoglobin in the blood leads to a parallel increase in CFT ($r = 0.517$; $p < 0.01$). A similar correlation was observed between BFR and serum iron and ferritin ($r = 0.66$; $p < 0.001$) and ($r = 0.45$; $p < 0.05$), respectively. These figures confirm that a positive correlation between ferrokinetic parameters and GFR has a positive effect on renal function (Figure 5). Therefore, the elimination of iron and ferritin deficiency in the body has a positive effect on the functional state of the kidneys, stabilizes the general condition of patients and improves

quality of life….

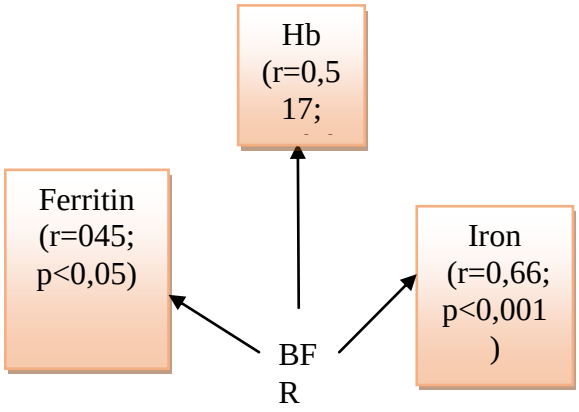


Figure 5.
A correlation between the rate of glomerular filtration rate and ferrokinetic parameters in patients with decreased left ventricular ejection fraction with chronic heart failure anemia.

The association between cystatin-C and ferrokinetic parameters, which have been widely used in the assessment of renal functional status in recent years, has shown that an increase in it in the blood leads to an increase in anemia.

In particular, an increase in cystatin-C in the blood leads to a reliable decrease in hemoglobin (r = -0.30) and serum iron and ferritin (r = -0.48 and r = -0.29) (p <0.05 in all cases) (Figure 6).).

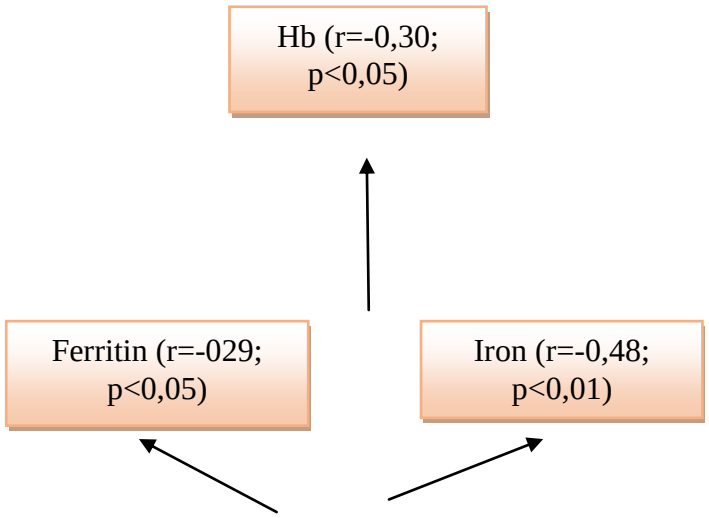


Figure 6.
Correlation between cystatin-C and ferrokinetic parameters in patients with decreased left ventricular hemorrhage fraction in anemia with chronic heart failure.

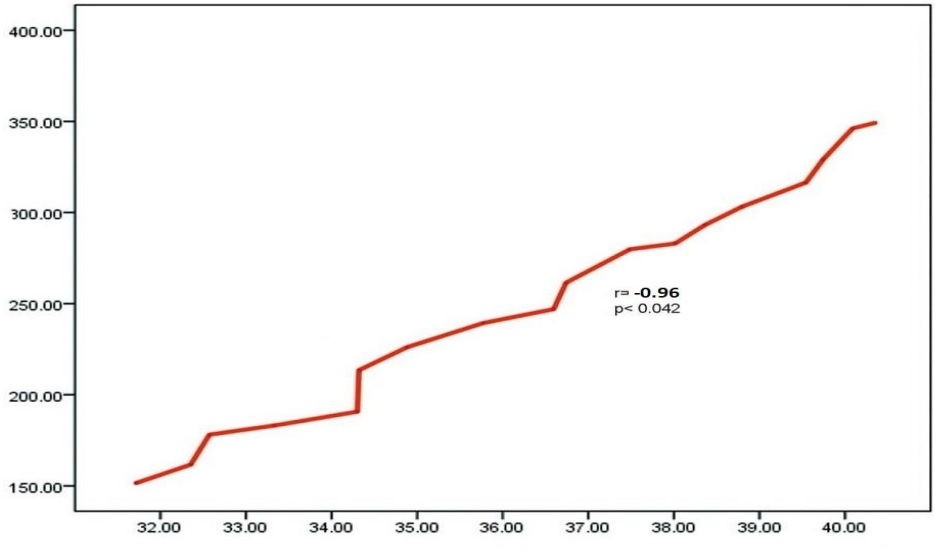
The results confirm that anemia is synchronized with an increase in cystatin-C levels in the blood and that they have an aggravating effect on each other.

It was also found that there was a negative correlation (r = -0.96; p <0.01) between the hemorrhage fraction and the endurance index in patients with decreased left ventricular hemorrhage fraction (Figure 7).

PSYCHOLOGY AND EDUCATION (2021) ISSN: 0033-3077 Volume: 58(4): Pages: 1265 - 1276
Article Received: 08th October, 2020; Article Revised: 15th February, 2021; Article Accepted: 20th March, 2021

Figure 7

a six-minute walking test(M)



Left ventricular fibrillation fraction(%)
Indications of correlation between left ventricular fibrillation fraction,and six walking test in patients with left ventricular fibrillation fraction, intermediate and decreased in chronic heart failure with anemia

Green -Remained
Blue-Intermediate
Red-Decreased

It has been confirmed in numerous studies that a decrease in the left ventricular hemorrhage fraction leads to a decrease in the level of endurance of patients to physical exertion.

The results confirmed that galectin-3 and TGF-β_1, which indicate fibrosis processes in the heart and kidneys, and aldosterone, a marker of fibrosis in both organs, increased in parallel when CHF was associated with anemia. At the same time, the increase in the marked markers was more pronounced in the CHF hemorrhage fraction, and was more pronounced in intermediate hemodynamic types, ie diastolic dysfunction. A clear reliable negative correlation between renal fibrosis marker TGF-β_1 and cystatin-C and ferrokinetic parameters was found in cases where CHF was accompanied by a decrease in left ventricular hemorrhage fraction. This confirms that the development of fibrous processes and an increase in the level of cystatin-C in the blood during anemia leads to an exacerbation of existing anemia. The results show that similar antianemic and antifibrosis treatments should be performed on the basis of standard treatment when CHF is accompanied by anemia.

Conclusion.1. An increase in galectin-3 levels in the blood led to a reliable decrease in the six-minute walking test in all hemodynamic types (preserved, intermediate, decreased) with chronic heart failure anemia.

2. A positive reliable correlation between aldosterone and galectin-3 in anemia in all hemodynamic types of chronic heart failure confirmed the synchronization of fibrous processes in the body.

3. An increase in galectin-3 in the blood resulted in a correspondingly reliable decrease in the six-minute walking test in all hemodynamic types (preserved, intermediate, decreased) with chronic heart failure anemia.

4.The negative correlation between ferrokinetic parameters with TGF-β_1, i.e. hemoglobin, iron and ferritins, has

been shown to have a mutually reinforcing effect.

5. High levels of aldosterone levels were detected in patients in the left ventricular hemorrhage fraction.

References

1.Atroshenko Ye. S. Patient with chronic serdechnoy nedostatochnost'yu i soxranennoy systolicheskoy funksiey levogo jeludochka / Ye. S. Atroshenko // Serdechnaya nedostatochnost '. - 2007. - T. 8. - 6. - P. 297-300.

2.Belyalov F. I. Treatment of internal diseases in the conditions of comorbidity: monogr. / F. I. Belyalov. - 8-e izd. - Irkutsk: RIO IGIUVa, 2012. - 285 C.

3.Gadaev A.G., Turakulov R.I., Kurbonov A.K. Occurrence of anemia in chronic heart failure and its negative impact on the course of the disease // Medical Journal of Uzbekistan. - 2019 - 2. - S. 74 - 77.

4.Gadaev A.G, Qurbonov A.K, Sabirov M.A, Sayfullayev M.B, Gadaeva N.A., Turakulov R.I. Assessment of Erythropoietin Levels and Correlation with Cytokines in Patients with Chronic Heart Failure // International Journal of Pharmaceutical Research. - 2021. - Vol 13R. 713-720.

5.Naumova L.A., Osipova O.N. Comorbidity: mechanisms of pathogenesis, clinical significance // Modern problems of science and education. - 2016. - 5. - P. 19-26.

6.EwansW. E. Pharmacogenomics - DrugDisposition, DrugTargets, and Side Effects / W. E. Ewans, H. L. McLeod // N. Eng. J. Med. - Vol. 3. - 2003. - Feb. - Vol. 48, N 6. - R. 538-549.

7.Bayliss E. A. Description of barriers to self-care by persons with comorbid chronic diseases / [et al.] // Annals of Family Medicine. - 2003. - Vol. 1. - 1. - P. 15-21.

8.Dickson V. V. A qualitative meta-analysis of heart failure self-care practices among individuals with multiple comorbid conditions / V. V. Dickson, H. Buck, B. Riegel // J. of Cardiac Failure. - 2011. - Vol. 17. - 5. - P. 413-419.

9.Fortin M. [et al.]. A systematic review of prevalence studies on multimorbidity: Toward a more uniform methodology // Annals of Family Medicine. - 2012. - Vol. 10. - 2. - P. 142-151.

10.Longjian L. Epidemiology of heart failure and scope of the problem // Cardiology Clinics. - 2014. - Vol. 32. - P. 1-8.

11.Garganeeva A.A., Bauer V.A., Borel 'K.N. Pandemic of the XXI century: chronic heart failure - bremya sovremennogo obshestva. Epidemiologicheskie aspekti // Sibirskiy medisinskiy zhurnal (Tomsk). - 2014. - P. 8-12; E-mail: borel.ks@ya.ru.

12.Vertkin A.L., Rumyansev M.A., Skotnikov A.S. Comorbidity in clinical practice. Chast '1. - 2011. Archive of internal medicine. - 2011. - (1). - S. 16-20.

13.Fortin M., Bravo G., Hudon C. etai. Prevalence of multimorbidity among adults seen in family practice // Ann. Fam. Med. - 2005. - 3. - P. 223-8.

14.Yefremova Yu.E. Lechenie otechnogo syndrome with chronic heart failure. RMJ. - 2015 - 27. S. 1622-1624.

15.Shah A.D., Langenberg C., Rapsomaniki E., et al. Type 2 diabetes and insaides of cardiovascular diseases: a cohort study of 1.9 million people. Lancet Diabetes Endocrinol. - 2015. - 3. - P. 105-13.

16. Lypez-Sendyn J. The heart failure epidemic // Mediographia. - 2011. - Vol. 33. - P. 363-369.

17.Shutov A.M., Yefremova Ye.V. Clinical features, quality of life and

prognosis of chronic cardiorenal syndrome // Nephrology. - 2015. - T. 19. - 2. - P. 64.
18.Lazebnik L.B. Starenie i polymorbitnost '// Consilium medicin - 2005. - 12. - P. 993-996.
19.Sharabchiev Yu.T., Antipov V.V., Antipova S.I. Komorbidnost '- aktual'naya nauchnaya i nauchno-prakticheskaya problema medisini XXI veka // Medisinskie novosti - 2014. - 8. - P. 6-11.
20.Gubanova G.V., Belyaeva Yu.N., Shemetova G.N. Komorbidniy patient: etapi formirovaniya, faktori riska i taktika vedeniya // Sovremennie problemi nauki i obrazovaniya. - 2015. - 6. URL: http: // science-education.ru/article/ view? Id = 23986.
21.Shukurov R.T., Abdullaev T.A. Gender differences and comorbidity in patients with chronic heart failure // Cardiovascular therapy and prophylaxis. - 2017. 16 (6). - S. 87-91.
22..Roig E . La anemia En La Insuficiencia cardiaca . ÏEsOON marcador degravedado objetiv oterapyutico OON? // Rev EspCardiol. - 2005. - Vol. 58. - P. 10-12.
23.Sharma R., Anker S. D. The 6-minute walk test and prognosis in chronic heart failure-the available evidence // Eur Heart J. - 2001. - Vol. 22. - P. 445-448.