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Imanmadiyeva DM, Dolinnaya VT

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Drug therapy for the treatment of chronic heart failure and concomitant diseases

T. V. Shapovalenko[1], N. M. Zinchenko[2], D. M. Imanmadiyeva[3], V. T. Dolinnaya[4]

This article discusses traditional tools and drug therapy in the treatment of chronic heart failure. The study investigates the drugs that both directly reduce the occurrence of new symptoms and prevent new concomitant diseases. The study investigates modern drugs for the treatment of concomitant diseases, as well as for the diagnosis of new ones. The authors consider the treatment of chronic heart failure with immune and other concomitant diseases using diabetes mellitus as an example. New data on the increased frequency of various types of mechanical myocardial dyssynchronicity (atrio-ventricular, interventricular and intra-ventricular) and their combinations in patients with chronic heart failure of ischemic origin, associated with type 2 diabetes mellitus, has been obtained. A relationship between the severity and type of chronic heart failure (depending on the functional class and left ventricular ejection fraction) and myocardial dyssynchronicity was established.

It was shown that an increase in the glycosylated haemoglobin levels was associated with an increase in the parameters of electrical and intra-ventricular mechanical dyssynchronicity. Data on the effects of cardiac dyssynchronicity on the structural and functional myocardial parameters in patients with chronic heart failure of ischemic origin and type 2 diabetes mellitus was further defined. The effects of myocardial dyssynchronicity on cardiac remodelling, occurrence of inadequate models of left ventricular geometry and diastolic function were defined.

Key words: chronic heart failure, ischemic origin, diabetes mellitus, treatment, cardiac function.

Medikation in der Behandlung der chronischen Herzinsuffizienz und Begleiterkrankungen. Kurzfassung: Der Beitrag befasst sich mit den medikamentösen Therapiemöglichkeiten der chronischen Herzlinsuffizienz. In vorliegender Studie wurden Arzneimittel, die sowohl Symptome direkt reduzieren als auch Begleiterkrankungen verhindern sollen, untersucht, wobei die Verfasser die Behandlung der chronischen Herzinsuffizienz mit Immun- und anderen Begleiterkrankungen am Beispiel von Diabetes mellitus in den Fokus stellten. Daraus resultierten aktuelle Daten zur erhöhten Häufigkeit verschiedener Ausprägungen der mechanischen myokardialen Dyssynchronizität (atrioventrikulär, interventrikulär und intraventrikulär) und deren Kombinationen bei Patienten mit chronisch ischämischer Herzinsuffizienz, assoziiert mit Diabetes mellitus Typ 2.

Es wurde die Verbindung zwischen dem Schweregrad und der Art der chronischen Herzinsuffizienz (abhängig von der Klassifikation und der linksventrikulären Ejektionsfraktion) und der Myokard-Dyssynchronie hergestellt. Es wurde gezeigt, dass der Anstieg der glykosylierten Hämoglobinspiegel mit dem Anstieg der Parameter der elektrischen und intraventrikulären mechanischen Dyssynchronie in Verbindung steht. Weiters wurden Daten zu den Auswirkungen der kardialen Dyssynchronie auf die strukturellen und funktionellen Myokardparameter bei Patienten mit chronischer ischämischer Herzinsuffizienz und Typ 2 Diabetes mellitus erhoben. Die Auswirkungen der myokardialen Dyssynchronie auf das kardiale Remodelling sowie das Auftreten unzureichender Therapie der linksventrikulären Geometrie und der diastolischen Funktion werden beschrieben. **Z Gefäßmed 2020 (4): 12–21.**

Schlüsselwörter: chronische Herzinsuffizienz, Ischämie, Diabetes mellitus, Behandlung, Herzfunktion

Introduction

Chronic heart failure is one of the most common diseases resulting in high mortality among cardiac patients and has extremely high treatment costs. According to the WHO, about 2–3% of the population in the world suffer from chronic heart failure [1]. Chronic heart failure syndrome is associated with a significant reduction in life expectancy, deterioration of its quality and high mortality with a significant number of cases of sudden cardiac death [2]. The main problem in the treatment of patients with chronic heart failure is the need for frequent hospitalizations due to decompensation, as well as a high rate of emergency medical care on an outpatient basis [3]. Therapeutic and diagnostic measures for patients with chronic heart failure are associated with huge costs for the healthcare system and society as a whole [4].

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From: [1]Department of Sports Medicine and Medical Rehabilitation, I. M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation; [2]Department of Physical Rehabilitation, Ergotherapy with Physical Education Course, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine; [3]Department of Pediatrics named after D. Tussupova, Semey Medical University, Semey, Republic of Kazakhstan; [4]Department of Propaedeutics of Childhood Diseases, Semey Medical University, Semey, Republic of Kazakhstan

Correspondence to: Tatyana V. Shapovalenko, Department of Sports Medicine and Medical Rehabilitation, I. M. Sechenov First Moscow State Medical University (Sechenov University), 119435, 2 Bolshaya Pirogovskaya Str., Moscow, Russian Federation; e-mail: shapovalenko4468@murdoch.in

Chronic heart failure is often associated with concomitant diseases, for example diabetes mellitus. A combination of chronic heart failure and diabetes mellitus is observed in one third of cases, and the incidence of chronic heart failure in patients with diabetes is 2–3-fold higher than that in individuals without diabetes [5]. A combination of these two pathologies significantly complicates the course of each disease. Cardiovascular pathology is a leading cause of death in patients with diabetes mellitus in almost all countries worldwide, which is more than 60%.

Considering the pathogenesis of the studied combination, it should be noted that there is an etiological relationship between diabetes mellitus and chronic heart failure [6]. A prolonged course of diabetes mellitus can contribute to the development of myocardial dysfunction and chronic heart failure, which is due to the potentiation of the following processes: cardiac autonomic neuropathy, endothelial dysfunction, dyslipidaemia, hypercoagulation and hyperproduction of pro-inflammatory cytokines; and is also caused by the direct effects of hyperglycaemia on myocardial function and morphology. The importance of this study is due to the need to reduce pathogenetic processes and define a high-quality treatment using modern drugs.

Literature Review

Many studies have shown that the prevalence of asymptomatic diastolic dysfunction in patients with diabetes mellitus is more than 50%, despite adequate glycemic control [7]. An experi-

mental study clearly demonstrated that increased expression of C-reactive protein enhanced left ventricular dysfunction and contributed to inadequate post-infarction left ventricular remodelling [8]. Unfavourable effects of C-reactive protein on the processes of left ventricular remodelling do not depend on the size of myocardial necrosis and may be associated with increased apoptosis, macrophage infiltration, expression of protein-1 and matrix metalloproteinase-9 by monocytes in the adjacent to myocardial infarction area. C-reactive protein is an anti-inflammatory "trigger" because it stimulates the production of interleukin-1, interleukin-6 and tumour necrosis factor-α by monocytes. However, increased concentrations of anti-inflammatory mediators are not associated with a corresponding increase in anti-inflammatory cytokines, which results in the inflammatory imbalance in the cytokine system [9].

One of the main reasons for the development and progression of chronic heart failure is coronary heart disease, which is mainly manifested by acute and chronic myocardial ischemia (stable and unstable angina pectoris). The heart suffers the largest damage in acute myocardial infarction, when an ischemic necrosis of the myocardial area occurs due to absolute or relative insufficiency of its blood supply, which results in the development of ventricular dysfunction (left ventricular dysfunction is more often), which is manifested as heart failure symptoms [10]. During acute local ischemia, myocardial cell death occurs due to necrosis and apoptosis, with the release of intracellular proteins of cardiomyocyte into the bloodstream, which triggers an inflammatory reaction [11].

Inflammatory cells, including neutrophils, monocytes, macrophages and lymphocytes, penetrate the tissue and remove dead myocytes. After an inflammatory response, cardiac fibroblasts proliferate and release extracellular matrix proteins, such as collagen I, to form a fibrous scar that replaces dead myocytes and serves to prevent rupture [12]. An increase in myocardial "stiffness" in fibrosis of both infarcted and intact myocardial areas contributes to diastolic dysfunction, which impairs the ability of the heart to increase its ejection [13].

As a result of "stretching" of the scarred area, which is not able to withstand the growth of intra-ventricular pressure, changes occur in unaffected parts of the ventricle, i.e. healthy cardiomyocytes hypertrophy and divide, adapting to new functioning conditions, which contributes to the process of cardiac remodelling [14]. Remodelling leads to structural and functional rearrangements in the myocardium and left ventricular chamber, associated with the presence of a section of post-infarction necrosis or scar, resulting in its impaired geometry (increase in the final diastolic and final systolic volumes) and decreased pumping ability (decreased ejection fraction), which contributes to the development and further progression of systolic and diastolic dysfunction [15]. Post-infarction remodelling is a complex mechanism and is triggered by the activation of neurohumoral (the renin-angiotensin-aldosterone system [RAAS]) and sympathetic nervous system, as well as cytokine-signalling pathways leading to the progression of chronic heart failure [16].

Chronic heart failure is strongly associated with inflammation in terms of pathogenesis, disease severity and prognosis [17]. Inflammatory mediators directly affect cardiomyocytes, fibroblasts and β-adrenergic receptors, resulting in hypertrophy, fibrosis and impaired contractility of the cardiac muscle, or induced by apoptosis through the stimulation of the corresponding genes. The balance between pro- and anti-inflammatory factors can have beneficial or harmful effects on the course of chronic heart failure [18]. Major pro-inflammatory cytokines that play a leading role in the development and progression of chronic heart failure include tumour necrosis factor-α, interleukin-1 and interleukin-6 [19].

In the post-infarction period, cytokines (TNF-α, IL-1β and IL-6) can mediate the reconstruction of infarction areas, including phagocytosis and resorption of necrotic tissue, cell survival, hypertrophy of surviving cardiomyocytes, degradation and synthesis of extracellular matrix components (collagen, integrin), proliferation of myofibroblasts, angiogenesis, vasculogenesis and, to a limited extent, proliferation of progenitor cells [20]. The consequences of cytokine activation can be favourable, that is, can result in reparation and restoration of myocardial function, or unfavourable, can trigger the process of cell apoptosis and cause an additional inflammatory reaction, that is, result in acute cardiac rupture or chronic dilatation and the development of heart failure, which increases mortality.

Materials and Methods

According to the purpose and objectives of the study, 140 patients with chronic heart failure of ischemic genesis, of functional class II–III according to NYHA classification, were examined at a clinical centre, of which 100 patients had chronic heart failure associated with type 2 diabetes mellitus. All patients gave their consent to examination. The inclusion criteria were:

1) Signs of chronic heart failure. To assess the severity of chronic heart failure (functional class II-III), the functional classification of chronic heart failure proposed by the New York Heart Association (NYHA) was used.
2) A verified diagnosis of coronary heart disease (myocardial infarction more than 12 months prior to inclusion).
3) Type 2 diabetes mellitus in the stage of compensation and subcompensation.
4) An informed consent of the patient to participate in the study.

The exclusion criteria were: acute inflammatory, infectious, oncological, immune diseases; chronic diseases in the acute stage; chronic non-specific lung diseases; diabetic ulcers and gangrene of the lower extremities; acute myocardial infarction and surgical interventions within 12 months prior to inclusion. The patients included 59 (42.1%) men and 81 (57.9%) women. The age of the patients was 55-78 years with the median of 70.0 years. The median body mass index was 29.05 kg/m^2, which corresponds to overweight, and only 19 patients (13.6%) had normal body weight. According to echocardiography, the median left ventricular ejection fraction was 49.65%, with a minimum of 33.97% and a maximum of 64.85%. The 6-minute walk test showed that the median value was 332.5 m (the values ranged from 155 m to 395 m). In the group of patients with type 2 diabetes mellitus, the median of the test values was 315.0 m, and in the group without diabetes it was 345.0 m.

Chronic heart failure of functional class II was diagnosed in 88 patients (62.9%) and of functional class III – in 52 patients (37.1%). All patients were diagnosed with arterial hypertension, of which 31 (22.1%) had grade 1 and 109 (77.9%) had grade 2 hypertension. The medians of systolic blood pressure were 162.5 mmHg, diastolic – 95.0 mmHg, mean arterial pressure was 124.07 mmHg, and pulse pressure was 70.0 mmHg. The history of type 2 diabetes mellitus ranged from 1 to 10 years; the median value was 6 years. Coronary heart disease was observed in all cases, which was confirmed by myocardial infarction more than 12 months before the examination.

The group of patients with chronic heart failure and type 2 diabetes mellitus (study group) did not differ in sex (women/men), age, time after the onset of myocardial infarction, median systolic, diastolic, mean and pulse pressure, as well as mean values of the functional class of chronic heart failure, from the group of patients without diabetes (control group) ($p > 0.05$). The patients with type 2 diabetes mellitus had significantly ($p < 0.05$) higher heart rate and BMI and significantly lower median LV ejection fraction and the 6-minute walk test distance compared to patients without type 2 diabetes mellitus. Time from diagnosis of type 2 diabetes mellitus ranged from 1 to 10 years, and the median was 6.0 years. The patients with diabetes mellitus (n = 100) had maximum and minimum concentrations of glycosylated haemoglobin from 5.60 to 8.0% with a median level of 7.0%.

The patients with chronic heart failure with a lower ejection fraction (EF < 40%) received standard therapy for chronic heart failure: an angiotensin-converting enzyme inhibitor (lisinopril 20-40 mg/day), a β-blocker (bisoprolol 5–10 mg/day), a mineralocorticoid receptor antagonist (spironolactone at a dose of 25–50 mg/day) and a diuretic (furosemide 20–40 mg/day). The patients with chronic heart failure with a preserved ejection fraction (EF > 40%) received standard therapy (for patients with chronic heart failure with a preserved ejection fraction and concomitant arterial hypertension): ACE inhibitor (lisinopril 20–40 mg/day), β-blocker (bisoprolol 5–10 mg/day) and a diuretic (furosemide 20–40 mg/day).

Results and Discussion

The study of the myocardial contraction synchronization parameters in the patients with chronic heart failure of ischemic genesis of functional class II–III and type 2 diabetes mellitus showed that 61 of 100 patients had mechanical cardiac dyssynchronicity, which indicated a high (61%) incidence of cardiac dyssynchronicity in this population. In the patients with heart failure of functional class II–III (n = 40), myocardial dyssynchronicity was observed in a smaller portion of the patients, i. e. in 16 patients (40%). A significant increase in the incidence of dyssynchronicity in the patients with chronic heart failure and type 2 diabetes mellitus by 21% ($p < 0.05$), compared to the patients with chronic heart failure without diabetes, indicates an increased risk of heart dyssynchronicity in type 2 diabetes mellitus patients with chronic heart failure.

Among all examined patients with chronic heart failure (n = 140), the rate of electrical dyssynchronicity, namely "widened" QRS complex >120 ms, was 17.14% (24 patients). The rate of the signs of mechanical dyssynchronicity was as follows: an increase in time from the onset of QRS to peak systolic velocity (Ts ≥ 100 ms) was observed in 51 patients (36.43%), an increase in the standard deviation of time from the onset of QRS to peak systolic velocity (Ts-SD ≥ 33 ms) was observed in 49 patients (35.00%), an increase in the aortic pre-ejection interval (APEI > 120 ms) was observed in 42 patients (30.00%), a decrease in the pulmonary pre-ejection interval (PPEI < 110 ms) was observed in 46 patients (32.86%), inter-ventricular mechanical delay (IVMD > 40 ms) was observed in 36 patients (25.71%), and left ventricular dyssynchronicity (LVFT < 40%) was observed in 24 patients only (17.14%). As shown in Table 1, the rate of electrical cardiac dyssynchronicity (QRS > 120 ms) in the patients with chronic heart failure of ischemic origin and type 2 diabetes mellitus was 2.80-fold higher ($p < 0.05$) compared to the patients with chronic heart failure of ischemic origin without diabetes.

Table 1. Frequency of detection of various signs of cardiac dyssynchronicity in patients with CHF based on DM type 2 status.

Signs	Patients with CHF and DM 2 (n = 100)		Patients with CHF without DM 2 (n = 40)	
	Abs. value	%	Abs. value	%
Electrical dyssynchronicity				
QRS, ms	21	21.00*	3	7.50
Intraventricular dyssynchronicity				
Ts, ms	42	42.00*	9	22.50
Ts-SD, ms	40	40.00*	9	22.50
APEI, ms	33	33.00	9	22.50
PPEI, ms	42	42.00*	4	10.00
Interventricular dyssynchronicity				
IVMD, ms	31	31.00*	5	12.50
Atrioventricular dyssynchronicity				
LVFT, %	17	17.00	7	17.50

*Confidence level ($p < 0.05$) in relation to the frequency of detection of dyssynchronicity signs in patients with chronic heart failure without diabetes.

In patients with chronic heart failure and type 2 diabetes mellitus, there was a significant increase in the incidence according to 5 indicators than in the group of patients with chronic heart failure without type 2 diabetes: the increase in Ts 1.87-fold ($p < 0.05$), Ts-SD 1.78-fold ($p < 0.05$), AREI 1.47-fold ($p < 0.05$), PPEI 4.20-fold ($p < 0.05$), and IVMD 2.48-fold ($p < 0.05$). The incidence of IVMD in the groups was almost the same. During a study of the rates of combined types of myocardial dyssynchronicity in all patients with dyssynchronicity (n = 77), it was found that the combination of intraventricular and interventricular dyssynchronicity (Ts-SD + IVMD) was most common in 25.97% of cases (20 people), the second was a combination of intraventricular and atrioventricular cardiac dyssynchronicity (Ts-SD+LVFT) in 15.58% (12 patients), followed by the association of atrioventricular and interventricular dyssynchronicity (LVFT+IVMD), found in 10.39% (8 patients), but the combination of all types of dyssynchronicity (Ts-SD+LVFT+IVMD) was found only in 3 patients (3.90%).

Table 2 shows that among patients with dyssynchronicity, the rate of the association of Ts-SD + IVMD and LVFT + IVMD was significantly higher 4.98-fold ($p < 0.05$) and 1.84-fold

Table 2. Frequency of combined types of cardiac dyssynchronicity in patients with chronic heart failure and dyssynchronicity based on DM type 2 status (n = 77).

Signs	Patients with CHF, CD and DM 2 (n = 61)		Patients with CHF and CD without DM 2 (n = 16)	
	Abs. value	%	Abs. value	%
Ts-SD+LVFT	8	13.11*	4	25.00
Ts-SD+IVMD	19	31.15*	1	6.25
LVFT+IVMD	7	11.48*	1	6.25
Ts-SD+LVFT+IVMD	3	4.91	0	0.00

*Confidence level ($p < 0.05$) in relation to the frequency of combined types of dyssynchronicity in patients with chronic heart failure without diabetes mellitus.

Table 4. Frequency of combined types of cardiac dyssynchronicity in patients with CHF, DM type 2 and myocardial dyssynchronicity (n = 61).

Signs	Patients with preserved LVEF > 40% (n = 42)		Patients with reduced LVEF ≤ 40% (n = 19)	
	Abs. value	%	Abs. value	%
Ts-SD+LVFT	4	9.52	4	21.05*
Ts-SD+IVMD	9	21.43	10	52.63*
LVFT+IVMD	5	11.90	2	10.53
Ts-SD+LVFT+IVMD	1	2.38	0	10.53*

*Confidence level ($p < 0.05$) in relation to the frequency of combined types of dyssynchronicity in patients with chronic heart failure without diabetes.

Table 3. Frequency of various signs of cardiac dyssynchronicity in patients with CHF, DM 2 type (n = 100) based on LVEF.

Signs	Patients with preserved LVEF > 40 % (n = 72)		Patients with reduced LVEF ≤ 40% (n = 28)	
	Abs. value	%	Abs. value	%
Electrical dyssynchronicity				
QRS, ms	14	19.44	7	25.00
Intraventricular dyssynchronicity				
Ts, ms	24	33.33	15	53.57*
Ts-SD, ms	22	30.56	14	50.00*
APEI, ms	23	31.94	10	35.71
PPEI, ms	29	40.28	13	46.46
Interventricular dyssynchronicity				
IVMD, ms	20	27.78	10	35.71
Atrioventricular dyssynchronicity				
LVFT, %	13	18.06	6	21.43

* Confidence level ($p < 0.05$) in relation to the frequency of dyssynchronicity signs in patients with preserved LVEF > 40%.

($p < 0.05$), respectively, in a cohort of patients with chronic heart failure and type 2 diabetes in relation to patients with chronic heart failure without diabetes. And the rate of Ts-SD + LVFT in the group with diabetes was significantly less by 1.91 times ($p < 0.05$). The combination of all types of dyssynchronicity in patients with chronic heart failure was not detected at all, in contrast to patients with chronic heart failure combined with type 2 diabetes mellitus, in which this combination occurred in 3 patients, which was 4.91% ($p > 0.05$).

Analysis of the frequency of dyssynchronicity markers in patients with chronic heart failure and type 2 diabetes mellitus (n = 100) showed that in patients with reduced LVEF ≤ 40% (n = 28), a significant increase in the incidence was observed only in 2 signs (Tab. 3) than in the group of patients with preserved LVEF > 40% (n = 72): the increased frequency of Ts 1.61-fold ($p < 0.05$), Ts-SD 1.64-fold ($p < 0.05$). The incidence of other dyssynchronicity markers in the groups was almost the same, which may indicate a high level of myocardial dyssynchronicity (as one of the important factors in the progression of chronic heart failure) not only in patients with systolic dysfunction, but also in patients with a preserved left ventricular ejection fraction. Therefore, we recommended echocardiography to identify dyssynchronicity markers in the early stages of chronic heart failure, even before the occurrence of impaired heart pumping function in patients with chronic heart failure and type 2 diabetes mellitus.

Among patients with myocardial dyssynchronicity, chronic heart failure with reduced LVEF ≤ 40% and type 2 diabetes mellitus (n = 19), the rates of the associations were as follows: Ts-SD + IVMD 2.21-fold ($p < 0.05$), Ts-SD + IVMD 2.46-fold ($p < 0.05$) and Ts-SD + LVFT+IVMD 4.42-fold higher than the respective combinations in patients with preserved LVEF > 40% (Tab. 4).

Therefore, in the patients with chronic heart failure and type 2 diabetes mellitus, the rate of electrical (QRS extension > 120 ms) dyssynchronicity was 2.80-fold higher ($p < 0.05$) and the rate of mechanical dyssynchronicity was higher (Ts 1.87-fold [$p < 0.05$], Ts-SD 1.78-fold [$p < 0.05$], AREI 1.47-fold [$p < 0.05$], PPEI 4.20-fold [$p < 0.05$], IVMD 2.48-fold [$p < 0.05$]); the rate of a combination of cardiac dyssynchronicity types also increased: Ts-SD + IVMD – 4.98-fold ($p < 0.05$), LVFT + IVMD – 1.84-fold ($p<0.05$) and the rate of a combination of Ts-SD + LVFT decreased 1.91-fold ($p < 0.05$), compared to the patients without diabetes. The association of all types of dyssynchronicity (TS-SD + LVFT + IVMD) was observed in 3 patients, and these were the patients with a combination of chronic heart failure and type 2 diabetes. In the patients with chronic heart failure with a decreased LVEF ≤ 40% and type 2 diabetes mellitus (n = 100), a significant increase in the rate of Ts (1.61-fold, $p < 0.05$) and Ts-SD (1.64-fold, $p < 0.05$) was observed, compared to the group of patients with preserved LVEF > 40%.

Among the patients with myocardial dyssynchronicity, chronic heart failure with a decreased LVEF ≤ 40% and type 2 diabetes mellitus, the rate of the following associations was higher (Ts-SD + IVMD – 2.21-fold ($p < 0.05$), Ts-SD + IVMD – 2.46-fold ($p < 0.05$) and Ts-SD + LVFT + IVMD – 4.42-fold) compared to the patients with preserved LVEF > 40%. The study of electrical dyssynchronicity in the patients with chronic heart failure (Tab. 5) showed that the concomitant type 2 diabetes mellitus contributed to an increase in the median value of the QRS complex by 25.00% ($p < 0.05$), Ts by 24.06% ($p < 0.05$), Ts-SD by 20.81% ($p < 0.05$) and IVMD by 2 ms ($p < 0.05$). The

Table 5. Characterization of dyssynchronicity in patients with chronic heart failure of ischemic origin.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_V
Study group – patients with CHF and CD 2 (n = 100)					
QRS, ms	0.106	0.10*	0.06–0.14	0.08	0.12
Ts, ms	96.52	88.95*	16.9–260	64.50	118.55
Ts-SD, ms	33.22	29.9*	6.3–88.9	21.95	41.93
LVFT, %	50.96	52.0	31–70	43.75	58.00
APEI, ms	123.63	115.0	50–320	102.00	133.25
PPEI, ms	101.49	112.0	50–144	83.00	115.25
IVMD, ms	22.08	1.0*	-32–233	-10.00	52.00
Control group – with CHF (n = 40)					
QRS, ms	0.093	0.08	0.06–0.14	0.08	0.10
Ts, ms	76.28	71.7	21.5–154	55.75	92.83
Ts-SD, ms	25.74	24.75	6.4–51.9	20.83	29.23
LVFT, %	53.68	54.0	35–72	46.75	61.25
APEI, ms	114.40	111.5	78–85	98.00	118.00
PPEI, ms	112.50	112.0	95–124	110.00	117.25
IVMD, ms	1.65	-1.0	-33–75	-17.00	8.00

*Confidence level ($p < 0.05$) in relation to indicators of patients with CHF without diabetes.

Table 6. Signs of myocardial dyssynchronicity in groups of patients with dyssynchronicity.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_V
Group I – patients with CHF, DM 2 and dyssynchronicity (n = 61)					
QRS, ms	0.112	0.12	0.06–0.14	0.09	0.14
Ts, ms	118.58	113.8	23–260	92.30	135.00
Ts-SD, ms	41.00	39.4*	9.5–88.9	30.50	47.70
LVFT, %	47.39	48.0	31–66	40.00	55.00
APEI, ms	134.03	122.0	50–320	107.00	145.00
PPEI, ms	91.58	90.0*	50–144	78.00	112.00
IVMD, ms	42.39	43.0	-27–233	0	61.00
Group II – patients with CHF without DM 2 with synchrony (n = 16)					
QRS, ms	0.102	0.10	0.07–0.14	0.08	0.12
Ts, ms	97.69	105.7	42.9–154	66.88	119.13
Ts-SD, ms	32.81	33.2	18.3–51.9	22.83	38.10
LVFT, %	46.81	46.0	35–67	37.75	53.50
APEI, ms	126.56	131.0	78–185	98.75	150.50
PPEI, ms	110.06	111.0	95–124	107.50	113.50
IVMD, ms	16.5	22.5	-33–75	-14.25	50.50

*Confidence level ($p < 0.05$) in relation to indicators of patients with CHF without DM and with synchrony.

Table 7. Values of dyssynchronicity markers in patients with heart failure and type 2 diabetes (n = 100) based on the duration from the moment of detection of diabetes.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_V
Duration of DM 2 type up to 5 years (n = 49)					
QRS, ms	0.104	0.10	0.06–0.14	0.08	0.12
Ts, ms	90.07	87.0	16.9–183.5	64.60	114.00
Ts-SD, ms	31.69	30.3	6.3–68.5	22.50	42.80
LVFT, %	51.57	53.0	32–70	45.00	58.00
APEI, ms	131.67	116.0	50–320	110.00	140.00
PPEI, ms	102.98	112.0	50–125	97.00	117.00
IVMD, ms	28.27	1.0	-30–233	0	54.00
Duration of DM 2 type from 6 to 10 years (n = 51)					
QRS, ms	0.107	0.12	0.06–0.14	0.08	0.12
Ts, ms	102.72	97.5	23.5–260	65.05	121.85
Ts-SD, ms	34.70	28.6	9.3–88.9	21.80	41.85
LVFT, %	50.37	52.0	31–66	43.00	57.00
APEI, ms	115.90	112.0	50–220	97.50	130.00
PPEI, ms	100.06	100.0	56–144	83.00	114.50
IVMD, ms	16.14	1.0	-32–137	-15.50	51.5

Group differences are not statistically significant.

Table 8. Values of dyssynchronicity in patients with CHF and type 2 diabetes mellitus (n = 100) based on the choice of therapy.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_V
With insulin (n = 35)					
QRS, ms	0.105	0.12	0.06–0.14	0.08	0.12
Ts, ms	89.17	88.0	37–173	65.05	108.45
Ts-SD, ms	29.25	27.2	12.1–63.2	21.80	34.60
LVFT, %	50.00	52.0	31–65	42.50	57.50
APEI, ms	128.86	116.0	50–320	98.00	145.50
PPEI, ms	99.51	100.0	67–138	83.00	112.00
IVMD, ms	29.60	12.0	-32–220	-17.00	55.50
Without insulin (n = 65)					
QRS, ms	0.106	0.10	0.06–0.14	0.08	0.12
Ts, ms	100.48	92.3	16.9–260	64.60	125.00
Ts-SD, ms	35.36	31.2	6.3–88.9	22.50	46.00
LVFT, %	51.48	52.0	32–70	45.00	58.00
APEI, ms	120.82	115.0	72–283	105.00	122.00
PPEI, ms	102.55	112.0	50–144	84.00	117.00
IVMD, ms	18.03	0	-30–233	-4.00	31.00

Group differences are not statistically significant.

median values of LVFT, APEI, and PPEI in the groups did not differ significantly ($p > 0.05$).

During the study of groups of patients with dyssynchronicity (Tab. 6), a considerable but not significant increase in the median QRS in patients of group I by 20.00% ($p > 0.05$) compared with group II of patients was revealed. Such changes in QRS indicate that the addition of type 2 diabetes mellitus in patients with chronic heart failure contributes to the expansion of the QRS complex and thereby the progression of conduction disorders and the development of heart block.

Comparison of Ts values did not show a significant difference between group I and II, but there was an increase in this indicator in patients with diabetes by 7.66% ($p > 0.05$). The median Ts-SD was higher in the group with chronic heart failure, type 2 diabetes mellitus and cardiac dyssynchronicity (39.4 ms) and significantly different compared to the group of patients without diabetes (33.2 ms) by 18.67% ($p < 0.05$).

The median APEI values in group II were slightly higher (131.0 ms) compared to patients of group I by 7.38% ($p > 0.05$). The median PPEI was the lowest in the group with heart failure

Table 9. Indicators of myocardial dyssynchronicity in patients with ischemic CHF and DM type 2 (n = 100) based on the level of glycosylated haemoglobin.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_V
$HbA1_c$ < 7.0 (n = 33)					
QRS, ms	0.095	0.09	0.06–0.14	0.08	0.12
Ts, ms	60.14	60.0	16.9–173	43.10	76.00
Ts-SD, ms	21.72	21.1	6.3–63.2	14.90	27.80
LVFT, %	50.73	53.0	31–70	40.00	58.00
APEI, ms	125.12	115.0	50–320	103.00	122.00
PPEI, ms	106.61	112.0	50–138	97.00	120.00
IVMD, ms	18.61	0	-26–233	-17.00	23.00
$HbA1_c$ ≥ 7.0 (n = 67)					
QRS, ms	0.111	0.12*	0.07–0.14	0.08	0.14
Ts, ms	114.44	107.7*	44.5–260	87.3	132.00
Ts-SD, ms	38.89	35.4*	15.1–88.9	27.60	46.10
LVFT, %	51.07	51.0	32–66	44.50	58.00
APEI, ms	122.90	115.0	78–250	102.00	133.50
PPEI, ms	98.97	110.0	50–144	79.50	115.00
IVMD, ms	23.79	6.0	-32–139	0	55.00

*Confidence level (p < 0.05) in relation to dyssynchronicity signs in the group of patients with glycosylated haemoglobin level $HbA1_c$ < 7.0.

Table 10. Values of cardiac dyssynchronicity signs in patients with CHF, DM 2 type and CD (n = 61) based on CHF FC.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_V
CHF FC II (n = 34)					
QRS, ms	0.110	0.12	0.08–0.14	0.08	0.14
Ts, ms	97.34	103.3	23–135	86.65	113.88
Ts-SD, ms	33.92	33.2	9.5–49.5	27.65	41.88
LVFT, %	48.94	50.0	31–66	40.25	55.00
APEI, ms	123.12	122.0	50–217	98.25	141.75
PPEI, ms	94.79	95.5	56–144	78.00	112.75
IVMD, ms	28.44	22.5	-27–139	0	53.50
CHF FC III (n=27)					
QRS, ms	0.115	0.12	0.06–0.14	0.10	0.14
Ts, ms	145.31	140.0*	60–260	113.05	173.00
Ts-SD, ms	49.93	47.0*	20.6–88.9	36.15	63.20
LVFT, %	45.44	44.0	32–60	37.50	51.50
APEI, ms	147.78	128.0	88–320	111.00	153.00
PPEI, ms	87.48	83.0	50–120	75.00	111.50
IVMD, ms	59.96	55.0*	-26–233	17.50	82.00

*Confidence level (p < 0.05) in relation to patients with CHF FC II

Table 11. Cardiac dyssynchronicity in patients with CHF, DM 2 type and CD (n = 61) based on LV ejection fraction.

Signs	Statistical data				
	M	Median	Min–Max	KWN	KWV
LVEF > 40% (n = 42)					
QRS, ms	0.111	0.11	0.08–0.14	0.09	0.14
Ts, ms	110.86	111.30	23–157	86.65	117.97
Ts-SD, ms	38.17	39.22	9.5–68.5	27.65	44.58
LVFT, %	47.76	47.51	31–66	39.25	55.00
APEI, ms	128.35	122.0	50–320	100.75	152.75
PPEI, ms	94.26	95.5	50–144	78.00	111.75
IVMD, ms	36.71	34.6	-27–233	0	62.25
LVEF ≤ 40% (n = 19)					
QRS, ms	0.114	0.14*	0.06–0.14	0.85	0.14
Ts, ms	169.9	172.53*	88.9–260	124.70	197.75
Ts-SD, ms	53.89	54.71*	30.6–88.9	40.70	65.55
LVFT, %	40.32	41.14*	32–60	43.00	51.50
APEI, ms	126.68	118.0	88–220	110.50	142.50
PPEI, ms	85.57	89.13*	50–119	70.00	113.00
IVMD, ms	58.32	60.1*	-26–137	12.50	78.50

*Confidence level (p < 0.05) in relation to patients with a preserved ejection fraction

combined with type 2 diabetes mellitus and heart dyssynchronicity (90.0 ms) and significantly different by 23.33% (p < 0.05) compared to the group of patients with chronic heart failure and dyssynchronicity (111.0 ms). The IVMD and LVFT values between groups I and II did not have significant differences (p > 0.05). During the analysis of cardiac dyssynchronicity signs in patients with CHF and DM type 2 based on the DM duration since the detection (Tab. 7), there were no significant (p > 0.05) differences in myocardial dyssynchronicity signs between groups with the 5-year duration of DM since the detection and the group of patients with the duration of type 2 diabetes mellitus from 6 to 10 years.

No significant (p > 0.05) discrepancies were found in the values of cardiac dyssynchronicity markers in patients who received oral hypoglycaemic drugs or insulin (Tab. 8).

When comparing groups of patients with CHF and diabetes based on the content of glycosylated haemoglobin (Tab. 9), significant differences were identified by three indicators: an increase in the group with glycosylated haemoglobin $HbA1_c$ ≥ 7.0 median QRS by 33.33% (p < 0.05), Ts by 79.50% (p < 0.05) and Ts-SD by 67.77% (p < 0.05) compared to the group of patients with the level $HbA1_c$ < 7.0.

Therefore, in patients with ischemic CHF and DM type 2, there is a significant increase in median Ts by 24.06% (p < 0.05), Ts-SD by 20.81% (p < 0.05), IVMD by 2 ms (p < 0.05), when compared with a group of patients with ischemic CHF without diabetes. Moreover, in patients with glycosylated haemoglobin $HbA1_c$ ≥ 7.0, a significant increase in dyssynchronicity markers was as follows: QRS by 33.33% (p < 0.05), Ts by 79.50% (p < 0.05) and Ts-SD by 67.77% (p < 0.05), compared with a group of patients with $HbA1_c$ level < 7.0. Based on the study of the importance of myocardial dyssynchronicity marker in a group of patients with ischemic CHF and DM type 2 and myocardial dyssynchronicity (n = 61), it was established that patients with FC III had more severe cardiac synchronicity disturbances compared to patients with CHF FC II (Tab. 10).

The analysis of mechanical dyssynchronicity in the patients with FC III showed a significant increase in Ts medians by 35.53% (p < 0.05), in Ts-SD by 41.57% (p < 0.05) and in IVMD by 144.44% (p < 0.05), compared to the patients with FC II. In the patients with FC III, a significant decrease in the median LVFT by 13.64% (p > 0.05) and PPEI by 15.06% (p > 0.05), and an

increase in APEI by 4.92% ($p > 0.05$) were observed, compared to the patients with FC II of chronic heart failure. The markers of electrical dyssynchronicity in the patients with FC II and III of chronic heart failure did not differ significantly ($p > 0.05$).

The study of CD depending on LVEF (Tab. 11) in the patients with chronic heart failure, type 2 diabetes and dyssynchronicity (n = 61) showed that the patients with decreased LVEF ≤ 40% (n = 19) demonstrated a significant aggravation of dyssynchronicity compared to the patients with LVEF > 40% (n = 42). The median values of both electrical dyssynchronicity (QRS > 120 ms, by 33.33% [$p < 0.05$]) and mechanical CD were significantly increased (intra-ventricular myocardial dyssynchronicity Ts increased by 55.01% [$p < 0.05$], Ts-SD by 39.49% [$p < 0.05$] and the median IVMD by 25.5 ms [$p<0.05$]). The APEI values did not significantly differ between the groups ($p > 0.05$). The patients with LVEF ≤ 40% also demonstrated a decrease in the median PREI by 6.67% ($p < 0.05$) and LVFT by 13.40% ($p < 0.05$), which indicated a further impairment of the synchronization of myocardial contraction.

The statistical analysis of electrical dyssynchronicity in the patients with CHF and type 2 diabetes mellitus, depending on the LV geometric models (Tab. 12) showed that the highest median values were observed in the group of patients with the most severe type of LV remodelling, i.e. in the patients with eccentric LV hypertrophy (group III) and the median was 20.00% ($p > 0.05$) higher compared to the patients with concentric LV remodelling, and 20.00% ($p > 0.05$) higher compared to the patients with concentric hypertrophy. At the same time, the patients with eccentric LV hypertrophy showed a significant increase by 142.99% ($p < 0.05$) in the median time from the onset of QRS to peak systolic velocity (Ts) compared to the patients with concentric remodelling and by 18.90% ($p < 0.05$) compared to the patients with concentric hypertrophy. In group II, a significant increase in Ts by 104.37% ($p < 0.05$) was observed compared to the patients from group III.

In group III, median Ts-SD was significantly higher, by 211.18% ($p < 0.05$), compared to group III and 79.32% ($p < 0.05$) higher compared to group II. In the patients with concentric hypertrophy, median Ts-SD was significantly higher, by 73.53% ($p < 0.05$), compared to the patients with concentric remodelling. No significant ($p > 0.05$) differences between such parameters of dyssynchronicity as APEI and LVFT were observed in the groups. The group of patients with eccentric hypertrophy showed a significant decrease in the median PREI values by 16.16% ($p < 0.05$) compared to the patients with concentric LV remodelling.

The highest median IVMD was observed in the group of patients with concentric hypertrophy with a significant difference from the median in the patients with concentric remodelling, by 17.0 ms ($p < 0.05$). In group III, median IVMD was 12.0 ms ($p < 0.05$) higher compared to the group. Therefore, in the patients with chronic heart failure of ischemic origin, type 2 diabetes mellitus and dyssynchronicity, an increase in the functional class from II to III results in a significant increase in Ts values, by 35.53% ($p < 0.05$), Ts-SD – by 41.57% ($p < 0.05$) and IVMD – by 144.44% ($p < 0.05$). This category of patients with a decrease in the ejection fraction (EF ≤ 40%) showed a significant increase

Table 12. Myocardial dyssynchronicity in patients with chronic heart failure of ischemic origin and type 2 diabetes, depending on the geometric models of the left ventricle.

Signs	Statistical data				
	M	Median	Min–Max	KW_N	KW_v
Group I – patients with LV concentric remodelling (n = 11)					
QRS, ms	0.099	0.1	0.08–0.12	0.08	0.12
Ts, ms	40.47	43.5	16.9–64.2	23.25	54.40
Ts-SD, ms	15.62	17.0	6.3–28.2	9.40	20.00
LVFT, %	50.82	52.0	37–63	44.00	57.50
APEI, ms	103.00	111.0	50–142	93.50	115.00
PPEI, ms	111.09	115.0	68–138	105.50	121.50
IVMD, ms	-7.91	-11.0	-23–21	-17.50	0
Group II – patients with LV concentric hypertrophy (n = 75)					
QRS, ms	0.106	0.10	0.06–0.14	0.08	0.12
Ts, ms	92.87	88.9	28–173	67.20	113.60
Ts-SD, ms	31.62	29.5	7.6–68.5	25.15	39.10
LVFT, %	51.51	52.0	31–70	43.50	58.00
APEI, ms	129.05	117.0	78–320	104.00	140.50
PPEI, ms	101.56	111.0	50–144	83.50	115.00
IVMD, ms	27.31	6.0	-32–233	-6.00	54.00
Group III – patients with eccentric LV hypertrophy (n = 14)					
QRS, ms	0.113	0.12	0.07–0.14	0.08	0.14
Ts, ms	160.09	105.7	88–260	131.50	192.83
Ts-SD, ms	55.62	52.9	26.4–88.9	44.13	67.90
LVFT, %	48.14	47.5	32–61	44.25	52.50
APEI, ms	110.79	112.5	83–147	97.25	117.25
PPEI, ms	93.57	99.0	55–119	74.50	114.75
IVMD, ms	17.64	1.0	-29–74	0	52.00

in QRS by 33.33% ($p < 0.05$), Ts by 55.01% ($p < 0.05$), Ts-SD by 39.49% ($p < 0.05$), IVMD by 25.5 ms ($p < 0.05$), as well as a significant decrease in the median PREI by 6.67% ($p < 0.05$) and LVFT by 13.40 % ($p < 0.05$) compared to the patients with preserved systolic function (EF > 40%) In the process of inadequate post-infarction LV remodelling and the occurrence of inadequate models of left ventricular geometry in the patients with chronic heart failure and type 2 diabetes, a significant increase in the markers of dyssynchronicity, i.e. Ts ($p < 0.05$), Ts-SD ($p < 0.05$), IVMD ($p < 0.05$), and a significant decrease in PPEI ($p < 0.05$) were observed.

The patients with chronic heart failure and preserved LV ejection fraction (EF > 40%) received standard therapy (for patients with chronic heart failure with preserved LVEF and concomitant arterial hypertension): ACE inhibitor (lisinopril 20–40 mg/day), β-blocker (bisoprolol 5–10 mg/day) and a diuretic (furosemide 20–40 mg/day). All patients additionally received acetylsalicylic acid at a dose of 75 mg/day and statins (atorvastatin – 10–20 mg/day). However, all patients with type 2 diabetes mellitus, according to international standards for the treatment of this disease) received biguanides (metformin at a dose of 1000 mg twice daily) and sulfonylurea derivatives (glibenclamide 5–10 mg/day) or, if necessary, insulin at a dose of 0.6–0.8 U/kg of body weight daily.

42 patients with type 2 diabetes and CHF with preserved ejection fraction (EF > 40%) and myocardial dyssynchronicity were selected and divided into two groups: group I (n = 20) –

Table 13. Change in diastole values after standard therapy (Me, [KW_N; KW_v]).

Signs	Standard therapy (n = 20)	
	Before treatment	After treatment
E, m/s	0.92 [0.72; 0.99]	0.92 [0.73; 0.99]
A, m/s	0.73 [0.62; 0.83]	0.76 [0.65; 0.87]
E/A	1.20 [1.11; 1.29]	1.16 [1.08; 1.24]
DT, ms	178.5 [164.3; 192.0]	184.5 [172.3; 197.85]
IVRT, ms	85.5 [77.0; 93.0]	88.0 [79; 95.8]

Group differences are not statistically significant.

Table 14. Changes in diastolic function parameters in patients of group II after inclusion of coenzyme Q10 into the standard therapy (E, [KW_N; KW_v])

Signs	Standard therapy + coenzyme Q10 (n = 22)	
	Before treatment	After treatment
E, m/s	0.9 [0.77; 1.0]	0.9 [0.75; 0.97]
A, m/s	0.78 [0.64; 0.89]	0.84 [0.71; 0.91]
E/A	1.13 [1.06; 1.22]	1.06* [1.02; 1.10]
DT, ms	172.0 [163; 180.5]	187.0* [179; 203.5]
IVRT, ms	82.0 [77.5; 89]	90.0* [84; 96]

*Confidence level ($p < 0.05$) in relation to the diastolic function values in patients before treatment with the inclusion of coenzyme Q10 into the standard therapy.

patients who received standard therapy and group II (n = 22) – patients who received standard therapy with coenzyme Q10 at a dose of 30 mg twice daily for 3 months. All patients were examined before and after a three-month course of treatment. The drugs were well tolerated by all patients. There were no side effects resulting in drug discontinuation. Changes in the parameters of diastolic function during standard therapy for 3 months in group I (n = 20) (Tab. 13) showed that the treatment did not result in significant changes in diastolic parameters.

Standard therapy for 3 months with coenzyme Q10 in the treatment of CHF of ischemic origin with preserved LV ejection fraction (EF > 40%), type 2 diabetes mellitus and myocardial dyssynchronicity (n = 22) (Tab. 14) resulted in a significant decrease in the medians of the E/A ratio by 6.60% ($p < 0.05$)

Table 15. Change in the values of the myocardial dyssynchronicity in group I after the standard therapy (Me, [KW_N; KW_v])

Signs	Standard therapy (n = 20)	
	Before treatment	After treatment
QRS, ms	0.12 [0.08; 0.12]	0.11 [0.08; 0.12]
Ts, ms	110.75 [93.98; 134.0]	106.0 [95.43; 122.88]
Ts-SD, ms	39.15 [30.53; 45.98]	34.8 [31.5; 41.23]
LVFT, %	49.5 [42.25; 57.25]	52.0 [46.25; 58.0]
APEI, ms	130.5 [114.25; 158.0]	122.0 [110.5; 146.0]
PPEI, ms	98.5 [78.0; 114.75]	100.0 [84.25; 113.0]
IVMD, ms	48.5 [0.0; 73.0]	34.0* [-1.75; 57.0]

*Confidence level ($p < 0.05$) in relation to the dyssynchronicity values in patients before the standard therapy.

Table 16. Change in the values of the myocardial dyssynchronicity in group II after inclusion of coenzyme Q10 into the standard therapy (Me, [KW_N; KWv])

Signs	Standard therapy + coenzyme Q10 (n=22)	
	Before treatment	After treatment
QRS, ms	0.12 [0.1; 0.14]	0.11 [0.1; 0.13]
Ts, ms	113.8 [90.5; 154.5]	106.7 [87.95; 128.3]
Ts-SD, ms	39.4 [30.5; 52.4]	34.4 [29.1; 37.5]
LVFT, %	44.0 [38.0; 51.5]	54.0* [42.5; 58.0]
APEI, ms	115.0 [96.0; 140.5]	111.0 [97.5; 126.0]
PPEI, ms	89.0 [77.0; 100.0]	100.0* [91.5; 110.0]
IVMD, ms	24.0 [3.0; 55.0]	18.0* [-1.5; 28.5]

*Confidence level ($p < 0.05$) in relation to the dyssynchronicity values in patients before treatment with the inclusion of coenzyme Q10 into the standard therapy.

and an increase in delay of early diastolic filling (DT) by 8.72% ($p < 0.05$) and time of isovolumic LV relaxation (IVRT) by 9.76% ($p < 0.05$).

The comparison of diastolic values in the patients with chronic heart failure with preserved ejection fraction (EF > 40%) and type 2 diabetes mellitus showed that in the patients who received a metabolic drug, coenzyme Q10, for 3 months together with standard therapy, an additional significant increase in the delay of early diastolic filling (DT) by 5.36% ($p < 0.05$) and

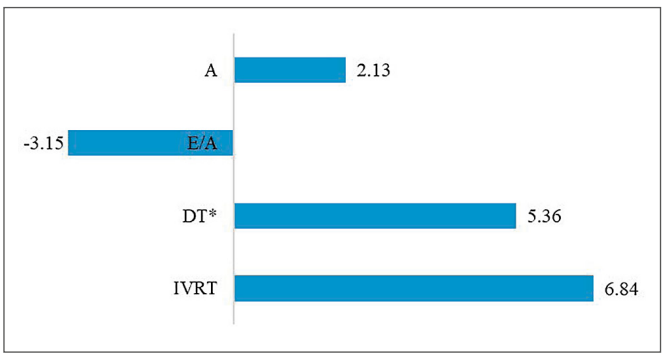

Figure 1. Effects of coenzyme Q10 on diastolic function in patients with ischemic chronic heart failure with preserved LV ejection fraction (EF > 40%), type 2 diabetes mellitus and myocardial dyssynchronicity.
*Significance level ($p < 0.05$) compared to diastolic function in the patients on standard therapy.

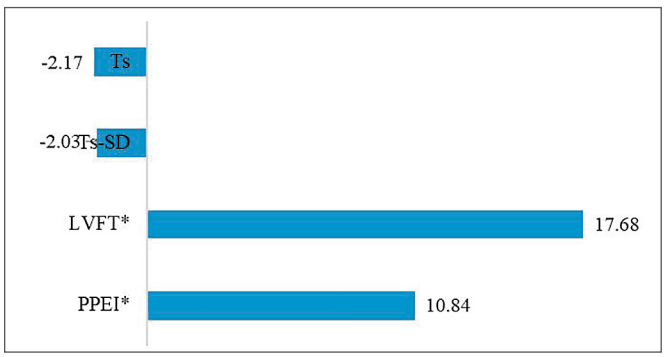

Figure 2. Effects of coenzyme Q10 on cardiac dyssynchronicity in the patients with ischemic chronic heart failure with preserved LV ejection fraction (EF > 40%), type 2 diabetes mellitus and myocardial dyssynchronicity.
*Significance level ($p < 0.05$) compared to diastolic function in the patients on standard therapy.

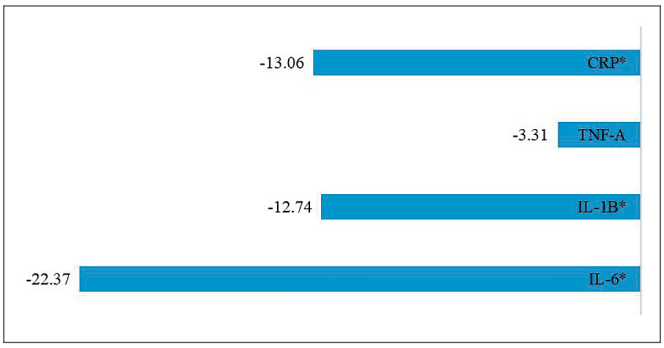

Figure 3. Effect of coenzyme Q10 on inflammation in patients with ischemic chronic heart failure with preserved LV ejection fraction (EF > 40%), type 2 diabetes mellitus and myocardial dyssynchronicity. *Significance level ($p < 0.05$) compared to diastolic function in the patients on standard therapy.

time of isovolumic LV relaxation (IVRT) by 6.84% ($p < 0.05$) was observed compared to the patients who received standard therapy only. The median maximum early peak velocity (E) in both cases remained unchanged (Fig. 1).

The analysis of myocardial dyssynchronicity in the group I patients receiving standard therapy (n = 20) showed a 42.65% decrease in IVMD (Tab. 15) ($p < 0.05$).

In group II, the patients (Tab. 16) who received coenzyme Q10 together with standard therapy (n = 22) showed significant differences in the following parameters of mechanical myocardial dyssynchronicity: median IVMD decreased by 33.33% ($p < 0.05$), while LVFT and PPEI increased by 22.73% ($p < 0.05$) and 12.36% ($p < 0.05$), respectively.

The patients who received coenzyme Q10 together with standard therapy showed an additional significant increase in the LVFT medians by 17.68% ($p < 0.05$) and PPEI by 10.84% ($p < 0.05$) compared to the patients who received standard therapy only. These changes indicate that additional therapy with coenzyme Q10 at a daily dose of 60 mg for 3 months improves the synchronous contractions of the chambers and myocardial segments, i.e. reduces cardiac dyssynchronicity (Fig. 2).

The study of the inflammatory parameters in the patients with CHF with preserved LVEF > 40%, type 2 diabetes and dyssynchronicity before and after 3 months of standard therapy (n = 20) showed a significant decrease in the median of one pro-inflammatory cytokine, TNF-α, by 41.05% ($p < 0.05$) (Tab. 17). A decrease in CRP by 7.07% ($p > 0.05$), interleukin-1β by 20.34% ($p > 0.05$) and interleukin-6 by 13.60% ($p > 0.05$) was significant, but not reliable.

The patients from group II who received coenzyme Q10 (n = 22) in addition to standard therapy showed a significant decrease in the median concentrations of all the studied inflammatory parameters (Tab. 18): CRP by 20.13% ($p < 0.05$), TNF-α by 44.36% ($p < 0.05$), IL-1β by 33.08% ($p < 0.05$), and IL-6 by 35.97% ($p < 0.05$).

The analysis of the above changes show that the inclusion of coenzyme Q10 in standard therapy at a dose of 60 mg daily for 3 months in patients with ischemic chronic heart failure with preserved ejection fraction (EF > 40%), type 2 diabetes mellitus and myocardial dyssynchronicity contributes to an additional significant decrease in the medians of C-reactive protein by 13.06%, interleukin-1β by 12.74% and interleukin-6 by 22.37% (Fig. 3), compared to the patients who received standard therapy only.

Table 17. Changes in concentrations of inflammatory markers in group I after the standard therapy (Me, [KW_N; KW_v])

Signs	Standard therapy (n = 20)	
	Before treatment	After treatment
CRP, mg/L	5.6 [4.88; 7.19]	5.23 [3.82; 6.29]
TNF-α, pg/mL	178.5 [111.6; 209.3]	126.55* [87.85; 156.05]
IL-1β, pg/mL	154.4 [93.05; 214.9]	128.3 [70.48; 169.35]
IL-6, pg/mL	164.6 [119.8; 219.4]	144.9 [106.7; 174.7]

*Confidence level ($p < 0.05$) in relation to the values of inflammation markers before treatment with standard therapy.

Table 18. Change in concentrations of inflammatory markers in group II after inclusion of coenzyme Q10 into the standard therapy (E, [KWN; KWV])

Tests	Standard therapy + coenzyme Q10 (n = 22)	
	Before treatment	After treatment
CRP, mg/L	5.37 [4.15; 7.28]	4.47* [3.25; 5.45]
TNF-α, pg/mL	161.4 [123.1; 186.0]	111.8* [82.25; 130.9]
IL-1β, pg/mL	123.9 [104.05; 179.25]	93.1* [75.65; 128.95]
IL-6, pg/mL	168.2 [119.35; 203.45]	123.7* [87.15; 166.75]

*Confidence level ($p < 0.05$) in relation to the values of inflammation markers before treatment with the inclusion of coenzyme Q10 into the standard therapy.

In patients with CHF with preserved LVEF > 40%, type 2 diabetes mellitus and dyssynchronicity, an inclusion of coenzyme Q10 in the standard therapy at a dose of 30 mg twice daily for 3 months contributed to a decrease in the intensity of symptoms associated with CHF. During the 6-minute walk test in the patients with ischemic heart failure with preserved EF > 40%, type 2 diabetes mellitus and dyssynchronicity before and after standard therapy, the median of this distance changed from 297 m to 332 m; this difference (increased by 10.54%) turned out to be unreliable ($p > 0.05$). In the patients who received additional coenzyme Q10, this difference was significantly higher by 16.71% ($p < 0.05$), with the median distance being 289 m before treatment and 347 m after treatment.

The study results showed that after 3 months of standard therapy in the patients with chronic heart failure of ischemic origin with preserved EF > 40%, type 2 diabetes and dyssynchronicity, a decrease in the functional class of chronic heart failure was observed in 3 patients (of them, in 2 patients, FC decreased from IIIIII to III and in 1 patient from FC III to II), which is 15.0% ($p > 0.05$), and after the inclusion of coenzyme Q10 in the standard therapy for 3 months, it was observed in 6 patients (of which, in 4 patients, FC decreased from II to I and in 2 patients from FC III to II), which is 27.27% ($p < 0.05$). Therefore, mean functional class of chronic heart failure decreased by 10% ($p > 0.05$) on

standard therapy, from 2.2 to 2.0; and in the patients with coenzyme Q10 added to treatment, this value decreased from 2.18 to 1.91, i.e., 14.14% ($p < 0.05$). During standard therapy the type of diastolic dysfunction changed in 1 patient – 5.0% ($p > 0.05$) (from a pseudo-normal type to a milder type – relaxation disturbance), and in the patients who received coenzyme Q10 at a dose of 30 mg twice daily for 3 months, this change took place in 4 patients, which is 18.18% ($p < 0.05$).

Conclusions

The study confirmed the relationship between the severity of chronic heart failure and dyssynchronicity in patients with type 2 diabetes mellitus, i.e. patients of functional class III demonstrated a significant ($p < 0.05$) increase in the Ts, Ts-SD, APEI and IVMD markers compared to patients of functional class II. A decrease in ejection fraction (EF < 40%) also resulted in impaired synchronization of heart contractions and a significant ($p < 0.05$) increase in QRS, Ts, Ts-SD, IVMD, as well as a decrease in PPE and LVFT compared to dyssynchronicity in patients with preserved EF > 40%.

Many randomized clinical studies showed that cardiac resynchronization therapy improved the functional class of chronic heart failure, exercise tolerance according to the results of the 6-minute walk test and quality of life, decreased the frequency of hospitalizations for chronic heart failure, mortality caused by chronic heart failure and overall mortality.

This study data confirmed that during the process of inadequate post-infarction left ventricular remodelling and the occurrence of inadequate models of left ventricular geometry, there was a significant ($p < 0.05$) increase in the concentrations of inflammatory markers in patients with chronic heart failure and type 2 diabetes. These effects were proven in the experiments on transgenic mice with overexpression of tumour necrosis factor-α in the myocardium, which resulted in a gradual myocardial hypertrophy and development of dilated cardiomyopathy, inflammatory cardiac cell infiltration and increased interstitial fibrosis.

Additional therapy with coenzyme Q10 in patients with chronic heart failure of ischemic origin with preserved EF > 40%, type 2 diabetes mellitus and dyssynchronicity resulted in a decrease in the inflammatory response, thereby slowing down the process of heart remodelling, positively affected the structural and functional parameters of the myocardium, synchronization of chamber and myocardial segment contraction, and slowed the progression of chronic heart failure. Therefore, the inclusion of coenzyme Q10 in a standard therapy at a dose of 60 mg/day for at least 12 weeks is feasible in this category of patients in order to correct impaired inflammatory response and asynchrony of heart contractions and improve the course of chronic heart failure.

Conflict of Interest

The authors declare that there is no conflict of interest.

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