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ABSTRACT

of the dissertation for the degree of Philosophy

FUNCTIONAL STATE OF THE HEART AND RHYTHM CHANGES IN PATIENTS WITH DIABETES MELLITUS AND PULMONARY TUBERCULOSIS

Speciality: 3228.01– Phthisiatry

Field of science: Medicine

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The work was performed at the Department of Pulmonary Diseases of the Azerbaijan Medical University, located under the Tuberculosis Dispensary No. 4, and at the Department of the Scientific-Research Institute of Cardiology named after J. Abdullayev.

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GENERAL DESCRIPTION OF THE WORK

Relevance of the topic. For today, despite the measures taken to combat tuberculosis, which is widespread in all countries of the world, this disease remains one of the most urgent problems of medicine[1]. Increasing the effectiveness of treatment of patients with diabetes mellitus and pulmonary tuberculosis, secreting multiple drug-resistant tuberculosis mycobacteria, is considered an urgent problem of modern phthisiatrics. According to the data of the World Health Organization, one person in the world is infected with tuberculosis every second, 1% of the population during the year.

According to WHO data, 10.4 million cases of tuberculosis were registered in 2015. According to the indicators of 2022, the number of patients suffering from tuberculosis in the world is 10.6 million. Of them, 5.8 million were men, 3.5 million were women, and 13 million were children. This disease is found in all countries of the world, in different populations. Treatment and prevention of the disease is possible[2]. At present, the issue that threatens the effectiveness of the measures aimed at improving the epidemic situation is the widespread spread of tuberculosis with high resistance to drugs. As the number of drug-resistant patients increases, the risk of infection spreading to healthy people and the number of cases of primary drug-resistant disease are high. 480,000 people were infected with multidrug-resistant TB, according to WHO figures in 2015[3].

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According to WHO, tuberculosis is one of the 10 leading causes of death in the world[4].

In recent years, special attention has been paid to the pathomorphosis of pulmonary tuberculosis, where extra-pulmonary pathologies create a background and join a specific process. One such disease is diabetes[5]. Pulmonary form of tuberculosis is more common in patients with diabetes mellitus (DM). In patients with diabetes mellitus, the exudative form of the tuberculosis process, which is mainly prone to fragmentation and bronchogenic dispersion, develops. Reparative processes are incomplete in severe diabetes. Failure to make an early diagnosis and ineffective treatment promotes the development of destructive forms of tuberculosis (infiltrative tuberculosis, caseous pneumonia, fibro-cavernous tuberculosis, tuberculoma) in patients with diabetes[6]. Diabetes mellitus is a risk factor for the development of pulmonary tuberculosis and its negative consequences. Despite numerous studies on the coexistence and interaction of SD and TB, data on the incidence of SD among TB patients in certain areas are conflicting[7].

Cardiovascular pathology is one of the main factors causing a high mortality rate among patients with tuberculosis and diabetes. In

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patients with tuberculosis and diabetes mellitus, such serious lesions of the heart as microangiopathy, myocardiodystrophy, vegetative diabetic cardial neuropathy, as well as atherosclerosis occur[8].

Idiopathic myocardiopathy is very common among patients with diabetes mellitus. In this case, damage to small vessels is observed (large collateral arteries are not damaged). Extravascular accumulation of collagen and triglycerides, myofibrillary accumulation of cholesterol occurs[9].

Clinically, myocardiopathy is characterized by a shortening of the left ventricular expulsion period, a lengthening of the tension period, an increase in diastolic volume. Changes characteristic of myocardiopathy can lead to heart failure in the acute period of myocardial infarction, which leads to a high percentage of mortality[10].

Myocardial infarction in such patients proceeds with specific signs: a large-area heart attack, thromboembolic aching, which leads to heart failure, repeated heart attack, a heart attack expressed in the absence of pain symptoms in the acute period.

Issues such as the relationship between cardiovascular system pathology and non-insulin-dependent diabetes mellitus have recently become one of the important problems of cardiology.

Taking into account the relationship between these diseases,

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their prospective rational treatment is of great interest in modern medical science. Taking into account the many unsolved issues and scientific questions, we conducted research with the following goal in mind.

Object and subject of research:

Patients with diabetes mellitus accompanying pulmonary tuberculosis. Insulin-dependent (type 1) and non-insulin-dependent (type ll) diabetes patients in different groups will be compared with tuberculosis patients without diabetes according to the functional and rhythm changes in the myocardium and the duration and severity of diabetes.

Purpose of the study:

The aim of conducting this study is to develop early detection, prevention and more effective complex treatment methods of heart functional status and heart rhythm changes in patients with diabetes mellitus accompanied by pulmonary tuberculosis.

The tasks of the research:

1. Diagnosis of heart rhythm and conduction disturbances in patients with diabetes mellitus with concomitant pulmonary tuberculosis.

2. Study of the relationship between central hemodynamics and external respiratory function disorders in pulmonary tuberculosis patients with concomitant diabetes mellitus.

3. Study of the influence of duration of diabetes mrllitus (up to 5 years, 5 years and more) on central hemodynamics and ventilation function of lungs in pulmonary tuberculosis patients with concomitant diabetes mellitus.

4. Study of the influence of the severity of diabetes mellitus on spirometry and echocardiographic parameters in patients with diabetes along with pulmonary tuberculosis.

5. Inclusion of third-generation non-selective α-,β-blocker cavedilol in the treatment scheme of patients with pulmonary tuberculosis and diabetes mellitus with heart rhythm disorders, and conducting observation and complex treatment measures on patients.

Provisions of the dissertation submitted for defense:

1. Study of the functional characteristics of the lungs and heart depending on the extent of morphological changes during diabetes

along with pulmonary tuberculosis;;

2. Assessing the impact of diabetes severity and duration on spirometry and echocardiographic parameters among patients concurrent diabetes and pulmonary tuberculosis

3. Inclusion of third-generation non-selective β-blocker carvedilol in the complex treatment scheme of patients with diabetes mellitus along with pulmonary tuberculosis and evaluation of the effectiveness of the drug.

Scientific novelty of the work:

- Changes in the functional state of the heart in patients with diabetes accompanied by pulmonary tuberculosis were studied depending on the severity of diabetes and the extent of lung damage.

- The interaction between disturbances of central hemodynamics and external respiratory functions in patients with diabetes mellitus accompanied by pulmonary tuberculosis was studied.

- The third generation non-selective α-, β-blocker carvedilol was included in the treatment scheme of patients with diabetes accompanied by pulmonary tuberculosis with heart rhythm and conduction disorders, observation and complex treatment measures were carried out on these patients.

Practical significance: Timely detection of the functional state of the heart and rhythm disturbances in patients with diabetes mellitus accompanying pulmonary tuberculosis, taking adequate, complex treatment measures.

Application of the research: The results of the research have been applied at the Anti-tuberculosis dispensaries N 4 in the city of Baku, and the Department of Pulmonary Diseases of the Azerbaijan Medical University.

The organization in which the dissertation work was carried out. The dissertation work was performed at the Department of Pulmonary Diseases of the Azerbaijan Medical University, Anti-Tuberculosis Dispensary No. 4 and the Scientific Research Institute of Cardiology named after J. Abdullayev.

Approval of research work: The initial discussion of the dissertation work was conducted at the Departament of

Phtisiology of the Azerbaijan Medical University (Protocol No.10; dated 26.04.2019).

The scientific seminar of the dissertation work was held at the scientific seminar of the BFD 4.17 Dissertation Council at the Azerbaijan Medical University (Protocol No.02; dated 01.03.2024).

The results of the research were discussed at various scientific conferences: III, V, VI Republican Scientific and Practical Conferences on Lung Diseases and Tuberculosis (Baku, 2010; 2011; 2013); International symposium dedicated to the 90th anniversary of National Leader Heydar Aliyev (Baku; 2013); Scientific conference dedicated to the 70th anniversary of A.A.Akhundbeyli (Baku; 2008); Scientific-practical conference dedicated to B.M.Ashurov's 70th anniversary (Baku, 2013) Scientific-practical conference dedicated to A.M.Aliyev's birthday (Baku; 2014); Scientific-practical conference dedicated to A.T.Agayev's 70th anniversary (Baku; 2014); a conference dedicated to the 95th anniversary of the birth of the outstanding ophthalmologist-scientist, academician Zarifa Aliyeva on "Modern achievements in healthcare" (Baku; 2018); XXV International Scientific and Practical Conference "Modern Medicine: New Approaches and Actual Researches" (Moscow, 2019); "Current Problems of Medicine" International Conference dedicated to the 100th anniversary of the birth of Professor Tamerlan Aliyev (Baku, 2021); Karabakh 3rd International Congress of Applied Sciences ("Year of Shusha-2022"); International scientific-practical conference "Actual Problems of Medicine" dedicated to the 100th anniversary of the birth of national leader Heydar Aliyev (Baku, 2023).

Published scientific works. The main provisions and results of the research were reflected in 28 scientific papers. 11 of them were scientific articles, 8 were published in local, 3 in foreign journals, 6 conference materials,11 theses – 1in foreign, 10 in local journals.

Scope and structure of the dissertation work. The dissertation consists of 169 pages of computer text (225,019 characters), introduction (10,423 characters), literature review (65,064 characters), Chapter “Materials and Methods” (31,196 characters), Chapter III

(28,213 characters), Chapter IV (23,280 characters), Chapter V (36,047 characters), conclusions (28,608 characters), results (2,824 characters), practical recommendations (1,011 characters) and a bibliography, including 202 sources (of which 13 domestic, 189 - foreign). The work is illustrated with 12 diagrams, 7 X-ray images and 29 tables.

MATERIALS AND METHODS OF THE RESEARCH

90 patients with pulmonary tuberculosis and diabetes received inpatient and outpatient treatment under our supervision at the Department of Phthisiatry of Azerbaijan Medical University located at the base of Baku City Anti-Tuberculosis Dispensary No. 4. Of these patients, 78 (100%) were included in the main group, and 12 patients were included in the control group (Fig. 1).

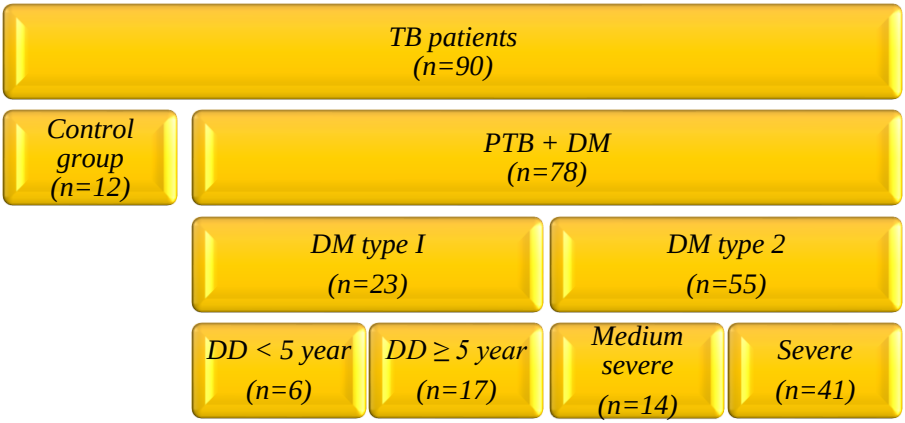


Fig. 1. Research groups

Of the 78 (100%) patients in the main group, 23 (29.5%) have insulin-dependent diabetes (IDDM, DM type1) and 55 (70.5%) have non-insulin-dependent diabetes (NIDDM, DM type 2). The control group included 12 patients with different forms of pulmonary tuberculosis without diabetes.

The vast majority of patients were between 31 and 50 years old, 17 (21.8%) of them were men and 14 (17.9%) were women.

The duration of tuberculosis in the main group fluctuated from 6 months to 10 years and more. 58 of the patients (74.4±4.9%) suffered from tuberculosis for more than one year, 20 of them (25.6±4.9%) had tuberculosis for more than 5 years. In 12 (15.4±4.1%) patients, the tuberculosis process was detected for the first time.

47 (60.3±5.5%) patients from the main group had various concomitant diseases. 14 of them (17.9±4.3%) had diseases of the digestive system. Diseases of the genitourinary system were recorded as a complication of diabetes in 12 patients (15.8±4.1%). Diseases of the eye and its accessory apparatus in 10 (12.8±3.8%) patients, diseases of the musculoskeletal system and connective tissues in 6 (7.7±3.0%) patients, nervous system diseases in 3 (3.8±2 ,2%), skin and subcutaneous tissue diseases were found in 2 (2.6±1.8%) patients.

In the majority of patients (56 people (71.8±5.1%)), the X-ray view of the disease was characterized by the presence of fibrous caverns. In addition, unilateral localization of the cavern was recorded in 45 (57.7%) patients and bilateral localization in 11 (14.1%) patients. Radiological changes in 29 (37.2±5.5%) patients were characterized by a large number of dissemination and cavities.

Cirrhotic changes limited to the lungs were found in 1 (1.3±1.3%) patient, exudative-inflammatory changes and foci of various degrees around the cavern were found in 36 (46.2±5.6%) patients. The infiltrative form of tuberculosis was detected in 48 patients, infiltrative pulmonary tuberculosis in the disseminated phase in 27 (34.6±5.6%) patients. In addition, the upper lobe segments of the lungs were damaged in 15 (19.2±4.5) patients on the right and in 12 (13.4) patients on the left side. With X-ray lobite was detected in 14 (17.9±4.3%) patients and bilateral infiltrative pulmonary tuberculosis which is in the destruction phase was detected in 9 (11.5±3.6%) patients by multi-axis radiography.

Cardiovascular changes were manifested as sinus tachycardia in 11 (14.1%) patients from the main group detected by electrocardiography. 8 (14.5%±4.8) of them had non-insulin-dependent diabetes mellitus (NIDDM), 3 (13.0±7.0%) had insulin-dependent diabetes mellitus (IDDM). Extrasystolic arrhythmia was detected in 17

(21.8%) patients, sinus bradycardia in 1 (1.3%) patient, and tachyarrhythmic rhythm disorders in 5 (6.4%) patients.

Laboratory examination methods were fully and sufficiently used in our study. Leukocytosis in the leukogram was determined in 46 (59.0±5.6%), changes in the leukogram of various combinations in 51 (64.4±5.4%) patients. Increased erythrocyte sedimentation rate was found in 49 (62.8±5.5%) patients, more than 40 mm/h in 23 (29.5±5.2%) patients. Elevation of C-reactive protein in 52 (66.7±5.3%) patients, decrease in albumin level and increase in globulin level in 28 (35.9±5.4%) patients were detected. A significant increase in the gamma fraction of globulins was observed. In order to study the functional state of the liver, total bilirubin (with its fractions), aminotransferase, and sugar levels were determined in the blood. Consequently, it was observed that 11 patients experienced a rise in bilirubin levels by 30 μm/l (with a range of 14.1%±3.9), while 10 patients showed an elevation in aminotransferase levels by 50-80 conditional units.

To detect impaired kidney function, we analyzed parameters including blood urea nitrogen (BUN), urine uric acid levels, and creatinine. This assessment enabled us to identify compromised renal excretory function related to nephropathy in 17 diabetic patients (21.8±4.7%).

Examination methods: In sputum examination, Levenstein-Yensen (DHT) solid nutrient medium, sensitivity to anti-tuberculosis drugs was determined by BacTek MGIT and GeneXpert MTB/RIF.

Blood glucose was determined by the ferricyanide method (Hagedorn-Jensen).

External respiratory function was determined by the spirography method on the "Jaeger" (Germany) device.

Electrocardiography was performed on the "Chanel ECG unit ECG-9801" device. In addition, ECG and daily monitoring (ECG-pro-Holter) were performed.

In radiography, Ikons (Germany) apparatus was used.

Cardiographic examinations were conducted on the "Copyright General Electric Co. 2003-Vivid 3" device for the assessment of intracardiac and intrapulmonary hemodynamic parameters.

Additionally, Doppler echocardiography was performed in impulse mode.

Pharmacological correction of arrhythmias. Arrhythmia and their combinations were treated with carvedilol. For the first 7 days of treatment, the dose was 3.125 mg 2 times a day, and for the next 7 days, the dose was increased to 6.25 mg 2 times a day. If the patients had no serious complaints, the dose was increased to 12.5 mg twice a day. In addition to carvedilol, the IC antiarrhythmic drug allapin (lappaconite hydrobromide) was prescribed to patients with IC grade arrhythmias. The duration of the treatment and the change of the dosage regime (increasing the dose) are determined by the doctor

Statistical analysis was carried out using variation (U-Wilcoxon (Mann-Whitney)), discriminant (χ^2 – Pearson criterion), correlation (Spearman's ρ-correlation), dispersion (ANOVA test) and cluster analysis methods. All calculations were made in EXCEL-2010 spreadsheet and SPSS-20 package program.

RESULTS OF THE RESEARCH

Heart rhythm disorders. 39 (50.0±5.7%) of the examined patients from the main group had heart rhythm disturbances. Sinus tachycardia was recorded in 11 (14.1±3.9%) patients. In addition, we found that in 6 (7.7±3.0%) patients, the pulse frequency did not correspond to the increase in body temperature and was observed even in the absence of fever. Sinus tachycardia with a pulse rate of more than 90 beats per minute was determined in 9 (11.5±3.6%) patients.

Extrasystolic arrhythmias were found in 17 patients in the main group, of which 10 (12.8±3.8%) had supraventricular extrasystoles, and 7 (9.0±3.2%) had ventricular extrasystoles. It should be noted that both supraventricular and ventricular type extrasystolic arrhythmias were observed in patients with chronic destructive tuberculosis with fibrosis changes and high alertness of the central nervous system and. It is the mechanical effect of the stretching caused by fibrosis on the heart that has led to the emergence of extrasystolic arrhythmias.

Tachysystolic atrial fibrillation was found in 4 (5.1±2.5%) patients with acute respiratory failure, including 1 (1.3±1.3%) patient with

cirrhotic changes in the lungs. Hypertrophy and dilatation of the right ventricle and atrium were detected in these patients.

Ventricular tachycardia was detected in 3 (3.8±2.2%) patients. The reason for this is the high degree of alertness of the central nervous system and the neuromuscular apparatus of the heart as a result of both toxic and mechanical effects in patients with pulmonary tuberculosis and diabetes. Ventricular tachycardia was recorded in 2 (2.6±1.8%) patients with bilateral fibro-cavernous tuberculosis and alcohol-induced cardiomyopathies.

ECG revealed 1 (1.3±1.3%) sinus arrhythmia, 1 (1.3±1.3%) sinus bradycardia.

Out of 11 (14.1±3.9%) patients with sinus tachycardia, 8 (10.3±3.4%) had non-insulin-dependent diabetes, and 3 (3.8±2.2%) had insulin-dependent diabetes.

26 (33.3±5.3%) patients from the main group had cardiac conduction disorders. In 11 (14.1±3.91%) patients, an atrioventricular conduction disorder was detected. Non-acute prolongation of PQ interval duration (0.2 seconds) was determined in 9 (11.5±3.9%) patients, which was associated with increased vagal nerve tone. In 2 patients, more noticeable disorders of conduction occurred as a result of damage to the conduction system.

Intraventricular conduction disorder was noted in 10 (12.8±3.8%) patients. Among these patients, right branch bundle blockade was observed in 8 (10.3±3.4%) patients. Depending on the width of the QRS complex, complete (0.10-0.12 seconds) and incomplete (more than 0.12 seconds) blockades were recorded in 3 and 6 cases, respectively. Blockade of the right bundle branch block had classic characteristics in 7 (9.0±3.2%) patients, which was manifested by the presence of a very small R wave in the 1st standard lead, a deep split S wave and a deep split R wave in the III standard lead. An atypical block (Wilson's block) was observed in 1 (1.3±1.3%) patient with a normal amplitude R wave and a small but wide S wave on the ECG.

As with heart rhythm disturbances, cardiac conduction disturbances have been reported more often in patients with non-insulin-dependent diabetes mellitus and have been associated with diabetic microangiopathy in the cardiovascular system and metabolic

disturbances, which are more prominent in this type of diabetes.

All patients underwent 24-hour Holter ECG monitoring during the first days of hospitalization. In 70% of cases, the fact that the rhythm disturbance is permanent has attracted special attention. Patients were monitored daily for 12 hours.

Supraventricular disorders were recorded the most, which accounted for 92.3%. In 34 patients from the main group (43.6±5.6%), supraventricular disturbances were manifested in the form of rare monotopic SVES (supraventricular extrasystole).

Polytopic SVES was recorded in 20 patients (25.6±4.9%), and group extrasystoles were present in 5 (6.4±2.8%) patients. Monofocal supraventricular tachycardia episodes were observed in 10 patients (non-insulin-dependent diabetes mellitus - 7 (12.7±4.5%), insulin-dependent diabetes mellitus - in 3 patients (13.0±7.0%)) and were not persistent. Permanent atrial fibrillation was recorded in 5 (6.4±2.8%) patients.

We detected ventricular rhythm disturbances in 50 (64.1±5.4%) patients. Among them, 20 (25.6±4.9%) patients (non-insulin-dependent diabetes - 14, insulin-dependent diabetes - 6) had a rare monotopic VES (class I VES). During Holter monitoring, 11-14 extrasystoles were recorded in 1 hour in these patients.

Episodes of allorhythmia with frequent monotopic VES were recorded in 21 (26.8±5.0%) patients (non-insulin-dependent diabetes mellitus - 16, insulin-dependent diabetes mellitus - 5). Polytopic VES was present in 9 (11.5±3.6%) patients (non-insulin-dependent diabetes mellitus-8, insulin-dependent diabetes mellitus-1). Heart conduction disorders were recorded in 28 (35.9±5.4%) patients. In the control group, rare monotopic VES was detected in only 2 (16.7%) patients during daily monitoring on ECG.

According to the above, 72 (92.3±3.0%) patients had different types of arrhythmias and blockages. 51 of them (65.4±5.4%) were patients with NIDDM, and 21 (26.9±5.0%) were patients with IDDM.

23 patients with pulmonary tuberculosis and insulin-dependent diabetes mellitus (IDDM) and 55 patients with non-insulin-dependent diabetes mellitus (NIDM) underwent echocardiographic and spirographic examination.

In patients with pulmonary tuberculosis and insulin-dependent diabetes, compared to the control group, the increase in the anterior-posterior dimensions of the right ventricle was 10.3% ($p<0.05$), the end-systolic dimension of the left ventricle was 7.1%, and the end-diastolic dimension of the left ventricle was 8.0% ($p<0.05$) was determined. Ejection fraction was lower - 18.0% ($p<0.001$) and pulmonary artery systolic pressure was increased by 10.3% ($p<0.01$) in people with pulmonary tuberculosis and diabetes.

It was found that pulmonary ventilatory function (PVF) in 78 patients with pulmonary tuberculosis and diabetes mellitus was significantly lower in patients with pulmonary tuberculosis and diabetes mellitus than in the control group (respectively 71.9±1.7% and 96.4±0.6 $p<0.001$). Spirographic parameters indicating bronchial airway patency disorders in diabetic patients were consistent. So, on average, FVC in the control group was 92.3±0.9%, and in patients with diabetes it was 60.8±1.2% ($p<0.001$). Similarly, FEV1 decreased and was 57.2±1.1% $p<0.001$ in patients with diabetes compared to 90.3±1.2% in the control group. We also found that the patency indicators of large and medium bronchi are low. At this time, FEF75 was 97.2±2.0% in the control group and 37.7±0.7% in the main group, the difference was statistically significant ($p<0.001$).

Central hemodynamics and ventilation function of the lungs were determined in the research groups. Patients with pulmonary tuberculosis and insulin-dependent diabetes mellitus were divided into 2 subgroups in order to determine the duration of the effect of diabetes mellitus on echocardiographic parameters: the 1st subgroup - duration of the disease up to 5 years; the duration of the disease in the 2nd subgroup was 5 years or more.

When analyzing the effect of duration of diabetes on echocardiographic parameters compared to the first subgroup, we found 19.6% (respectively 49.8±1.4%, $p<0.001$) reduction in the EF in patients with a disease duration of 5 years or more. An increase in the anterior-posterior diameter of the right ventricle by 10.8% (respectively, 32.1±0.9, $p<0.05$), the thickness of the ventricular wall by 29.3% (respectively, 12.2±0.5, $p<0.001$), the systolic pressure in the pulmonary artery by 20.4% (30.9±0.7 $p<0.001$, respectively) was observed.

Supraventricular disorders were detected in 4 (66.7±19.2%) patients in subgroup I and 17 (100%) patients in subgroup II, the difference was statistically significant (p=0.099). In subgroup II, supraventricular tachycardia was recorded in 3 (17.6±9.2%) patients: in 2 patients – group and pair SVES; In 1 patient – atrial fibrillation. Ventricle disorders were present in 10 (58.8±11.9%, p=0.549) patients: in 4 patients – rare monotopic VES; In 5 patients – dense monotopic; In 1 patient – polytopic VES. Conduction disorders occurred in 6 (35.3±11.6%, p=0.737) patients: Ventricular blockades were registered in them. Combined disorders were observed in 11 (64.7±11.6%, p=0.121) patients.

Compared to the control group, FVC in patients with pulmonary tuberculosis and type 1 SD was 92.3±0.9%, in patients with type 2 SD it was 57.1±2.3% (p<0.001). Similarly, FEV1 decreased, it was 90.3±1.2% in the control group and 54.1±1.3% in the main group (p<0.001). We also found that the permeability indicators of large and medium bronchi are low. At this time, FEF_{75} (35.8±1.5%, p<0.001) differed from the indicators of the control group (97.2±2.0%).

When the ventilatory function of the lungs (VFL) was studied in the research groups, it was determined that the VFL was statistically significantly lower in the main group compared to the control group (p<0.001) (Table 1).

Table 1

Ventilatory function of lungs in research groups

Spirometry indicators	The norm	Main group (n=78)	Control group (n=12)
VC, %	>80	73,9±1,7 (43-97) ***	96,4±0,6 (93-99)
FVC, %	>80	60,8±1,2 (44-85) ***	92,3±0,9 (86-98)
$FEV_{1,}$ %	>75	57,2±1,1 (41-73) ***	90,3±1,2 (84-97)
$FEF_{25,}$ %	>80	46,7±0,9 (34-62) ***	79,9±2,2 (70-91)
$FEF_{50,}$ %	>80	39,6±0,8 (28-54) ***	88,7±1,5 (78-95)
$FEF_{75,}$ %	>80	37,7±0,7 (26-48) ***	97,2±2,0(91-118)
Index Tiffnoi:	>70	58,7±1,3 (42-79) ***	72,7±2,0 (62-88)

Note: statistical integrity of the difference with control group indicators: *– p < 0.05;** – p < 0.01; *** – p < 0.001

We examined 55 (70.5±5.2%) patients with non-insulin-dependent diabetes mellitus and pulmonary tuberculosis. The coexistence of diabetes and pulmonary tuberculosis is accompanied by more pronounced remodeling processes of the myocardium. 5.0% increase in left ventricular end-systolic size compared to the control group (32.7±0.5 $p<0.05$ respectively), 7.5% increase in left ventricular end-diastolic size (49.7±0.8 respectively) increase was recorded, which indicates myocardial relaxation. In that group of patients, an accurate increase in the end-systolic size of the left ventricle and a decrease in the ejection fraction of the left ventricle by 17.4% (52.1±0.8 $p<0.001$, respectively) were recorded, which indicates a violation of myocardial contractility (Fig. 4.3). At the same time, an accurate increase of the anterior-posterior dimensions of the right ventricle by 10.1% (32.1±0.5 $p<0.05$, respectively) was recorded.

FEV_1 in patients with pulmonary tuberculosis and non-insulin-dependent diabetes mellitus was statistically lower than in the group of patients without diabetes (56.4±1.7 and 90.3±1.2%, respectively; $p<0.001$). The statistical integrity of spirography changes in other studied indicators was also low.

When the correlations between respiratory parameters and the duration of diabetes were analyzed, it was found that there was a negative relationship between FVC and the duration of DM (duration of DM up to 5 years: $r= - 0.58$; $p=0.003$; DM- duration of 5 years and more: $r= -0.65$; $p=0.014$).

A nonparametric correlation was carried out between the study groups with the determination of the Spirmen coefficient. With the help of this method, we found out the influence of pathogenetic factors on the development of dysrithmogenesis and the significant interaction between them. There was a positive ($R=0.07$; $p=0.538$) correlation between ventricular extrasystole (sparse monotope) and Inter-ventricular septal thickness, positive ($R= 0.104$; $p=0.366$) correlation between right ventricular wall thickness and negative ($R=-0.076$; $p=0.510$) correlation between FEV1. Positive correlation between dense as well as polytope and group SVES and interventricular septum thickness ($r=0.075$; $p=0.514$), positive with

right ventricular thickness (r=0.38; p=0.744) and some indicators of ERF: there was a negative correlation between vital capacity of the lungs (r=-0.203; p=0.075), FVC (r=-0.103; p=0.346) and FEV1 (r=-0.201; p=0.077). Indicators of ERF with anterior-posterior size of right ventricle: vital capacity of lungs (r=-0.066; p=0.565), FVC (r=-0.085; p=0.439), FEV1 (r=-0.027,p=0.813) there was a negative relationship between the indicators. There was a negative correlation between pulmonary artery systolic pressure and all parameters of ERF, and a positive correlation between right ventricular wall thickness. In patients with non-insulin dependent diabetes mellitus and pulmonary tuberculosis, we found a negative correlation between FVC and left ventricular end systolic size (r=-0.05; p=0.656), left ventricular end diastolic size (r=-0.110; p=0.337), right ventricular anterior-posterior size (R=-0.089; p=0.439). Cluster analysis allowed us to divide all patients into a certain number of clusters. Mathematically, we got 2 clusters.

The scores in each cluster were totaled and the structure of rhythm disturbances was determined. Cluster 1 to cluster 2 were averaged.

In cluster 1 patients, EchoCG indicators were at the upper limit of normal, while ERF indicators were relatively low. In cluster 2 patients, there was an increase in the thickness of the interventricular septal wall (p=0.008), the growth of the right ventricle and its hypertrophy, a decrease in the ejection fraction (p=0.018), an increase in the systolic pressure in the pulmonary artery (p=0.012), a decrease in ERF indicators. (FVC-p=0.021). ERF indicators were lower in cluster 2 than cluster 1 (FEV1- $p<0.001$; Tiffino index - $p<0.001$). Although there were differences in other indicators, they were not observed with statistical integrity.

We determined the effect of treatment on the dynamics of heart rhythm disturbances based on Holter monitoring indicators after treatment measures. To study the antiarrhythmic effect of carvedilol, we assigned a daily dose of 3,125-12,5 mg to the main group (n=78) patients.

20 of the patients (6 patients-IDDM and 14 patients-NIDDM) were prescribed the drug for 8 weeks, and the remaining 58 patients

were prescribed carvedilol as a course treatment for 6 months. For the first 7 days of treatment, the dose was 3.125 mg 2 times a day, and for the next 7 days, the dose was increased to 6.25 mg 2 times a day. Since no serious complaints were registered in the patients during this period, the dose was increased to 12.5 mg twice a day. A group of patients was prescribed the IC antiarrhythmic drug allapin (lappaconite hydrobromide) along with carvedilol based on the appointment of a cardiologist. The duration of the treatment and the change of the dosage regimen (increase in dosage) are determined by the doctor. In the first week of treatment, the drug was prescribed once a day at 25 mg, and if the therapeutic effect was low, prepatat was prescribed at 25 mg twice a day.

Patients received 6.25 mg of carvedilol after 24-hour ECG recording on the background of Holter monitoring. If necessary, the dose of the drug was increased to 12.5 mg. The effect is considered "good" when the absolute number of extrasystoles drops by 75%, and "satisfactory" when the absolute number of extrasystoles drops by 50-75%.

During Holter monitoring, 4 out of 6 patients with IDDM (66.7±19.2%) had supraventricular disturbances, in 2 patients (33.3±19.2%) ventricular disturbances, in 1 (16.7±15.2%)-conduction disturbances, in 1 (16.7±15.2%) - combined disturbances. Of 14 patients with type 2 SD, 11 (78.6±11.0%) had supraventricular disturbances before treatment, 1 (7.1±6.9%) had supraventricular tachycardia, 4 (28.6±12.1 %) had ventricular disorders, conduction disorders in 3 (21.4±11.4%), combined disorders in 3 (21.4±11.4%).

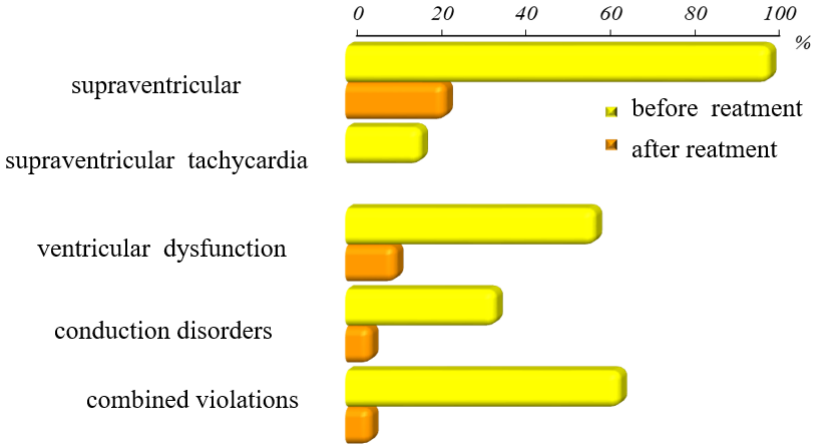
According to ECG changes 8 weeks after treatment, supraventricular disturbances were recorded in 3 (21.4±11.0%) patients, ventricular disturbances in 1 (7.1±6.9%) patient.

A 6-month course of treatment with carvedilol was administered to 58 patients (IDDM-17 patients, INDDM-41 patients) with pulmonary tuberculosis and diabetes. The drug was prescribed after breakfast at 09.00 to 55 (70.5±5.2%) patients, initially 6.25 mg, then 12.5 mg, and to 3 patients (3.5±2.2%) with severe tachycardia (heart rate 120 beats/min) at a dose of 25 mg.

In the control of SVES, "good" effect was found in 60.3% of

patients (DM 1type - 11 people, DM 2type - 27 people), "satisfactory" effect was seen in 35.3% (DM 1type - 4 people, DM 2type - 9 people). in 14.4% (DM1 type - 2 people, DM 2 type - 5 people) patients had no effect.

It should be noted that in patients with type 1 SD, supraventricular disturbances occurred in 17 (100%) patients before treatment, and in 4 patients – after treatment (23.5±10.3%, $\chi 2=17.9$; $p0<0.001$), in patients with type 2 SD was observed: before treatment - in 40 (97.6±2.4%) patients, after treatment - in 8 (19.5±6.2%, $\chi 2=48.3$; $p0<0.001$) (Graph 1).

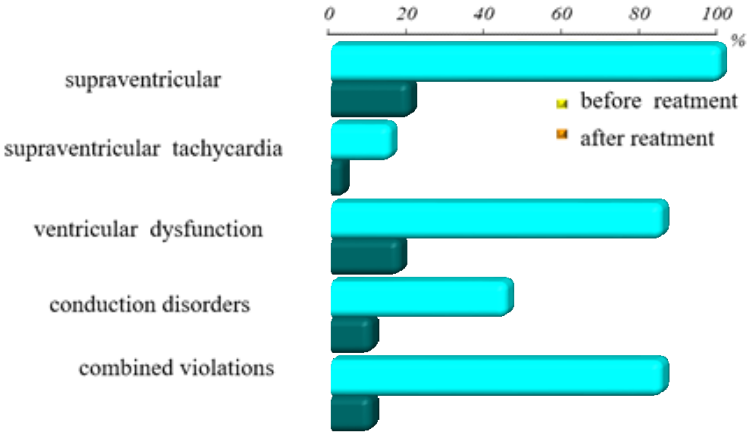


Graph 1. Changes in heart rhythm and conduction disturbances as a result of a course of treatment with carvedilol in patients with type 1 DM

4 patients with tachysystolic atrial fibrillation decreased to 1 patient on the background of taking carvedilol.Ventricular disorders: rare monotopic VES- before treatment in 4, after - in 1, dense monotopic VES - before treatment - in 5, after - in 1, polytopic VES - before treatment - in 1 patient. No VES was observed after treatment.

Conduction disorders: intraventricular blocks - before treatment - 6, after - 1 patient, combined disorders: before treatment - 11, after -

1 patient, the effect occurred only when the dose of allapinine was increased to 25 mg, and carvedilol to 12.5 mg. The peak respiratory rate increased by more than 15% in 48 patients and by 10% in 10 patients against the background of basic therapy during treatment. We compared the results of antiarrhythmic treatment after 8 weeks of carvedilol and 6 months of treatment.



Graph 2. Changes in cardiac rhythm and conduction disturbances as a result of a course of treatment with carvedilol in patients with type 2 DM

Tachysystolic atrial fibrillation decreased from 4 patients to 1 patient after taking carvedilol. Ventricular disorders: rare monotopic VES - before treatment in 11, after - in 1, dense monotopic VES - before treatment - in 4, after - in 4, polytopic VES - before treatment - in 8 patients, after treatment - in 2 patients was observed.

As a result of our research, we determined that the anti-arrhythmic effect of the drug was recorded in all patients in the first weeks, but this effect was even higher during the 6-month course of treatment with carvedilol. This is probably related to parallel anti-inflammatory treatment, broncholytic treatment, correction of diabetes, anti-tuberculosis treatment, normalization of homeostasis, metabolic disturbances, reduction of hypoxemia. In addition, we

concluded that the drug is effective against both supraventricular and ventricular arrhythmias. Taking the drug as a course of treatment for 6 months is more effective than taking it for 8 weeks.

Changes in indicators of central hemodynamics and external respiratory function against the background of the course of treatment with carvedilol. When central hemodynamic indicators were studied based on EchoCG indicators, it was found that in patients with pulmonary tuberculosis and diabetes treated with carvedilol, the systolic pressure in the pulmonary artery near the end of the observation period was 12.3% (respectively in DM type 1- 7.7% ($p<0.001$); in DM type 2 - 4.6% ($p < 0.01$) decreased. Also, the ejection fraction in these patients significantly increased after treatment (DM 1 type - 9.7% and DM 2 type -7.0%, $p<0.001$). During treatment, the dimensions of heart chambers and cavities were also right ventricular wall thickness (type 1 SD 2%, type 2 SD 0.9%, respectively), right ventricular anterior-posterior dimension type 1 SD 6.6%, type 2 SD 4.3 % has changed.

In 17 patients with insulin-dependent diabetes mellitus, according to the Echo CG indicators, the ejection fraction increased as a result of the treatment course with carvedelol (respectively, before treatment 49.8±1.4 ($p < 0.001$), after 54.6±1.6 ($p < 0.01$)), reduction of systolic pressure in the pulmonary artery (respectively, before treatment 31.9±0.7 ($p < 0.001$), after 29.4±0.6 ($p < 0.001$)), reduction of right ventricular anterior-posterior dimension (respectively, before treatment 32.1±0.9 ($p < 0.05$), after treatment - 30.0±0.7 ($p < 0, 05$)), decrease of the end systolic size of left ventricle (respectively, before treatment 34.5±1.0 ($p < 0.05$), after - 33.4±1.0 ($p < 0.05$)), decrease of left ventricular end-diastolic size (respectively, before treatment 49.8±1.3 ($p < 0.05$), after treatment - 47.5±1.0 ($p < 0.05$)), relative reduction of the thickness of the interventricular septum (respectively, before treatment 12.2±0.5 ($p < 0.001$), after - 11.3±0.5 ($p < 0, 01$)) was observed.

In 41 patients with non-insulin-dependent diabetes mellitus, according to Echo CG indicators, an increase in the ejection fraction as a result of a course of treatment with carvedelol, 51.9±1.0 ($p < 0.001$) - before treatment, and 55.6±1.0 ($p < 0.001$) - after treatment, a relative decrease in systolic pressure in the pulmonary artery (respectively, before treatment 27.7±0.3 ($p < 0.01$), after - 26.4±0.3

(p < 0.01)), reduced right ventricular anterior-posterior size (respectively, before treatment 32.1±0.6 (p < 0.05), after treatment - 30.7±0.5 (p<0.05)), left ventricular end-systolic size (respectively, before treatment 32.7±0.6 (p < 0.05), -31.4±0.6 (p < 0.05)), a relative decrease in left ventricular end-diastolic size (respectively, before treatment 49.7±1.0 (p < 0.05), after - 48.0±1.0 (p < 0.05)), a relative decrease the thickness of the interventricular septum (respectively, before treatment 10.0±0.2 (p < 0.05), after 9.5±0.2 (p < 0.05)).

No significant worsening of ERF after treatment was observed in patients with pulmonary tuberculosis and diabetes treated with carvedilol. Against the background of treatment, there was a tendency to limit restrictive changes in the lungs and improve bronchial permeability. Thus, during treatment with carvedilol, the Tiffno index increased in type 1 SD patients, 50.6±1.9% before treatment, 56.9±2.5% after treatment (p<0.001); increased in patients with type 2 SD, 59.8±1.8% before treatment and 65.8±1.9% after treatment (p<0.001) was calculated.

Thus, in our study, carvedilol showed high antiarrhythmic activity in relation to both ventricular arrhythmias and supraventricular arrhythmias in patients with pulmonary tuberculosis and diabetes. When using Carvedilol, deterioration of bronchial permeability and deepening of restrictive disorders are not observed in patients, which is explained by the pharmacological properties of the drug.

After a 6-month course of treatment with carvedilol as part of the complex treatment, shortness of breath decreased in the patients, interruptions in heart activity did not bother the patients anymore. According to HM ECG indicators, the normalization of HR was recorded. Pulmonary hypertension decreased, systolic and diastolic functions of the right and left ventricles improved. Indicators of ERF, blood oxygenation have improved significantly.

CONCLUSIONS

1. Based on the indicators of daily ECG monitoring, various heart conduction and rhythm disorders were detected in the main group of 78 (100%) patients with diabetes along with pulmonary tuberculosis. Ventricular disorders were found in 64.1±5.4% of patients, conduction

disorders in 35.9±5.4%. More supraventricular arrhythmias were observed, which were recorded in 92.3±3.0% of patients. [9,13,14,17,18, 23,24,25].

2. Each examined patient was assigned a complex of echocardiographic parameters. Compared to the control group, patients with diabetes mellitus accompanied by pulmonary tuberculosis had a decrease in APDRV, LVESS, LVEDS and EF, and significant higher SPPA. Spirographic parameters indicating bronchial conduction disorders were appropriate in diabetic patients. Thus, the average FVC in the control group is 92.3±0.9%; in patients with diabetes it was 60.8±1.2% ($p<0.001$). [1,2,4,5,6,8,16,20 ,21].

3. When the correlations between respiratory parameters and duration of diabetes were analyzed, it was found that there was a negative correlation between FVC and duration of diabetes (duration of diabetes up to 5 years: $r = -0.58$; $p =0.003$; duration of diabetes 5 years and more: $r = -0.65$; $p=0.014$). More severe changes in echocardiographic parameters were determined in patients whose disease duration was 5 years or more compared to the control group [7,10,19].

4. FEV1 in patients with pulmonary tuberculosis and SD type 2, depending on the severity of the disease, had low statistical integrity (respectively, moderately severe 61.9±2.4%; severe 56.4±1.7 $p<0.001$). Statistical significant was also low in the variation of other indicators studied by spirography. [11, 12, 27].

5. The introduction of the third generation non-selective β-blocker carvedilol into the treatment scheme of patients with diabetes mellitus along with pulmonary tuberculosis, in addition to the antiarrhythmic effect, had a positive effect on central hemodynamics, which was manifested in significant lowering of pulmonary hypertension in patients of the same category, significant increase in the left ventricular ejection fraction. We observed a more effective effect of the 6-month course of treatment with carvedilol in relation to SE (60.3%) during the 8-week administration of the drug. [3, 15, 22, 26,28].

PRACTICAL RECOMMENDATIONS

1. Certain frequency of cardiac rhythm and conduction disturbances in patients with pulmonary tuberculosis and diabetes mellitus,

especially in patients with arrhythmias that are not favorable for prognosis, requires wide application of daily ECG monitoring.

2. Dividing patients into clusters depending on certain clinical-instrumental parameters allows to accurately study dysrhythmogenesis.

3. The approach to the treatment of diabetic patients with pulmonary tuberculosis accompanied by heart rhythm and conduction disorders should be complex, and taking into account the long-term specific therapy in this group of patients, the observation of resistance to anti-tuberculosis drugs, along with specific antibacterial treatment, correction of blood sugar levels, diuretics, broncholytics, mucolytics should be used.

4. In patients with frequent polytope and group supraventricular and ventricular extrasystoles, as well as in tachysystolic forms of atrial fibrillation, it is recommended to use III generation non-selective α-,β-blockers for the normalization of heart rate.

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LIST OF ABBREVIATIONS USED

ACE — angiotensin-converting enzyme
AH – arterial hypertension
AP — arterial pressure
APDRV — anterior-posterior dimension of the right ventricle
AV — atrioventricular
CDPT — chronic destructive pulmonary tuberculosis
COPD– chronic obstructive lung disease
CPHD – chronic pulmonary heart disease
CT — computed tomography
DM — diabetes mellitus
DPA — the diameter of the pulmonary artery
ECG — electrocardiogram
ECHO-CG — echocardiography
EF — ejection fraction
ERF – external respiratory function
FEF — forced expiratory flow
FEF25 — forced expiratory flow at 25% of the pulmonary volume
FEF50 — forced expiratory flow at 50% of the pulmonary volume
FEF75 — forced expiratory flow at 75% of the pulmonary volume
FEV1 – forced expiratory volume in 1 second
FVC – forced vital capacity
HR — heart rate
IDDM- insulin-dependent diabetes mellitus
IHD — ischemic heart disease
IVS — interventricular septum
LVEDS — left ventricular end-diastolic size
LVESS — left ventricular end-systolic size
LVWT — left ventricular wall thickness
MB — Mycobacterium tuberculosis
NB — the number of breaths
NIDDM - non-insulin-dependent diabetes mellitus
SVES — supraventricular extrasystole
SPPA — systolic pressure on the pulmonary artery
TIS — the thickness of the interventricular septum
VCL – vital capacity of the lungs
VES— ventricular extrasystole
WHO – World Health Organization

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