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Evaluation of Clinical and Instrumental Results of Lung Examination in Patients with Diabetes Mellitus, Coronary Artery Disease, and Obesity

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Abstract

BACKGROUND: There are a large number of works devoted to the study of the state of the bronchopulmonary system in diabetes mellitus (DM) in the literature in the past 20 years. However, these studies are often conflicting. Some researchers identify a deterioration in the function of external respiration and a connection with metabolic changes and complications of the disease, others associate it with vascular pathology. There are a number of reports of increased pulmonary ventilation in diabetes.

AIM: This study aims to assess the structural and functional state of the lungs in patients with DM and in combination with coronary heart disease and obesity.

METHODS: A total of 395 patients with type 1 and type 2 DM were under observation. The diagnosis of DM was verified in accordance with international programs and was based on the WHO criteria. The glycemic level of patients was determined using a One Touch® basic glucometer (Johnson & Johnson, USA). The degree of carbohydrate metabolism compensation was assessed by the level of glycated hemoglobin, determined using a laboratory analyzer DCA-2000 MT (BAYER, Germany). The concentration of C-peptide in the blood serum was determined by the method of immunoluminometric analysis "Immunotech" (Czech Republic). Caro and HOMA-insulin resistance (IR) indices were calculated to identify and assess the IR. The indices of hormone metabolism were determined by ELISA using DSL kits (USA) with subsequent measurement of optical density on a Spectra Classic reader from Tecan (Austria): Corticotropic hormone (CTG), adrenaline, noradrenaline, cortisol, free hydrocortisone; 17-ketosteroids, 17-oxycorticosteroids, glucagon, insulin, somatotropic hormone; thyroid stimulating hormone (TSH); thyroxine (T_4); and thyroxine (T_3).

INSTRUMENTAL-FUNCTIONAL AND RADIATION RESEARCH METHODS: X-ray methods for lungs examining, computer spirography, and fibrobronchoscopy of the bronchi were performed in all patients. Morphological changes were assessed using histological and morphometric methods.

RESULTS: Pathogenetic mechanisms of the bronchopulmonary system disorders in patients with type 1 DM are associated with a decrease in the function of external respiration due to the volumetric air flow rates of the predominantly central airways and an increase in bronchial resistance. Alveolar hypoventilation of a restrictive type with impaired diffusion of gases through the alveolar-capillary membrane was detected in patients with type 2 DM. Restrictive and obstructive type disorders with impaired ventilation-perfusion ratios and pulmonary blood flow are formed in patients with type 2 DM combined with coronary artery disease and obesity.

CONCLUSIONS: (1) A decrease in the function of external respiration due to the central respiratory tract and an increase in bronchial resistance were noted in 38.4% of patients with type 1 DM. Restrictive alveolar hypoventilation was registered in 23.3% of patients with type 2 DM and catarrhal endobronchitis – in 21.31% of patients with type 2 DM. (2) Damage and fibrosis of the alveolar tissue, damage to the endothelium, and disorganization of the connective tissue of the lungs were characteristic of microscopic examination of the ultrastructure of the lungs in patients with DM.

Introduction

Researchers studying the effect of metabolic control on the function of external respiration have conflicting results [1], [2]. A number of publications indicate the absence of a relationship between carbohydrate metabolism and spirography, although the duration of diabetes had a negative correlation [3]. The reflection of hormonal and metabolic correlations in patients with diabetes mellitus (DM) is the relatively frequent involvement of the lungs in the pathological process, manifested by a variety of functional and morphological changes, which is of fundamental importance in the pathogenesis of lung diseases. There are few works devoted to a comprehensive assessment of the state of the bronchopulmonary system depending on the type of DM and the stage of the disease, some of them cover separate fragments [4], [5], [6], [7], [8]. And also, a number of authors point out the importance of

environmental and industrial factors, their influence on the formation of diseases of the respiratory, digestive, and circulatory organs, with morphofunctional changes in organs and systems [9], [10], [11], [12], [13], [14]. A population study in Denmark, including 3200 individuals, showed a negative correlation between plasma fasting glycemia, forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) [14]. The best indicators of FVC and FEV_1 were in persons on intensified insulin therapy, in comparison with persons receiving twice combined insulin, by more than 15% [15]. Impaired respiratory function (RF) in DM is associated with hyperglycemia. Thus, an increase in glycated hemoglobin (HbA1c) by 1% is accompanied by a decrease in FVC by 4%. Glycemia of 23–25 mmol/l for 6 weeks led to an increase in the number of vesicles in the capillary endothelium of experimental animals, contributed to the development of alveolar collapse and interstitial edema of the lung tissue [16].

Aim

This study aims to assess the structural and functional state of the lungs in patients with DM and in combination with coronary heart disease (CHD) and obesity.

Materials and Methods

A total of 395 patients with type 1 and 2 DM and control group C (25 practically healthy individuals) were divided into groups: 87 patients of the group with DM2 with CHD, 54 patients of the comparison groups CIHD (without DM2), 153 patients with DM2 and obesity, and 45 patients of the comparison group Co (with obesity without diabetes). The age of 56 patients with DM1 and the control group C1 (24 practically healthy individuals) averaged 37.5 ± 1.68 years. The duration of DM1 was in the range from 5 to 22 years – an average of 11.43 ± 0.32 years. The mean age of patients with DM2 and the control group C2 was 53.74 ± 2.48 years. The average duration of the disease in patients with DM2 was 9.2 ± 0.61 years. The age of patients with DM2 and CHD, comparison groups CCHD (without DM2) and Co (with obesity) averaged 60.1 ± 2.98 years. Duration of diabetes from 6 to 10 years was registered in 35 (12.72%) patients, from 10 to 15 years – in 151 (55.63%) patients, more than 15 years – in 88 (31.63%) patients. In the studied patients, the Rose questionnaire [18], [19], [20] recommended by the WHO for detecting of exertional angina, anamnestic data on hospitalization with angina pectoris or myocardial infarction, data from daily monitoring of ECG, EchoCG was used for screening. The mean duration of CHD was 10.7 ± 1.47 years. Angina pectoris of the IInd functional class was noted in 50 patients (50.0%), the IIIrd functional class – in 23% of patients, and the IVth functional class – in 9.0% of patients. There was a history of myocardial infarction in 18 (18.0%) patients. Patients of the DM2 groups with CHD received antianginal therapy and beta-blockers.

According to the criteria of the International Diabetes Federation [21], [22] (2005), abdominal obesity is diagnosed with a waist circumference of more than 94 cm in European men and more than 80 cm in women. Body mass index was calculated according to the WHO body mass classification (1997). The level of glycemia in patients was determined using a One Touch® Basic glucometer (Johnson and Johnson, USA). The degree of carbohydrate metabolism compensation was judged by the level of Hb_{A1c}, determined using a laboratory analyzer DCA-2000 MT (BAYER, Germany). A set of laboratory and biochemical methods of lipid and protein metabolism by enzymatic colorimetric methods (CHOD-PAP and GPO-PAP) were carried out on an automatic biochemical analyzer «TARGA-2000» («BIOTECHNICA INSTRUMENT», Italy). Blood serum enzymes (according to Reitman and Frenkel): Aspartate aminotransferase, alanine aminotransferase (AlAT), and lactate dehydrogenase were determined to assess the functional state of internal organs [23], [24].

All patients underwent a questionnaire to identify complaints from the respiratory system and a physical examination of the lungs. None of the patients with DM presented complaints from the respiratory organs and did not have a history of chronic bronchopulmonary diseases. About 9.2% of the examined patients smoked 5–10 cigarettes per day, 5.8% smoked occasionally [25].

Instrumental-functional and radiation research methods

X-ray methods of research

X-ray of the chest organs in two projections according to the generally accepted technique was performed in all groups.

Computer spirography

It was conducted spirography with the definition of 28 indicators reflecting the RF. The study of RF was carried out using an automated spirometric breath analyzer «AD-02» (National Center for Occupational Health and Occupational Diseases of the Ministry of Health of the Republic of Kazakhstan, Karaganda) based on a Pentium-III computer. When interpreting the obtained data, we were guided by the recommendations [26], [27], [28]. The study was conducted on an empty stomach in conditions of relative rest, in a sitting position.

The following indicators were determined to assess the state of the function of external respiration

in the examined patients: Vital capacity (VC), FVC, FEV_1, Tiffno index (FEV_1/FVC), maximum volumetric velocities (MVV) of exhalation at lung volumes equal to 25%, 50%, and 75% (MVV_{25}, MVV_{50}, and MVV_{75}), average expiratory volume velocity at lung volumes from 25% to 75% (AVV_{25-75}), and peak volumetric velocity (PVV). To detect bronchospasm, the patient was inhaled with Berotek and repeated spirography was performed 20 min after inhalation. An increase in indices by 15% or more indicates the reversibility of bronchial obstruction [29], [30]. For the analysis, the percentage of the obtained data to the proper values was determined, guided by the «Instructions for the use of spirographic indicators of the All-Russian Research Institute of Pulmonology» (Leningrad, 1986).

Fibrobronchoscopy examination of the bronchi was performed in the morning on an empty stomach under local anesthesia with a BF-P20 fiber-optic bronchoscope (Olympus, Japan) according to the generally accepted method. The prevalence of changes in the bronchial mucosa and the degree of inflammation were determined according to the classification of Lemoine (2002).

The obtained data were processed by the method of variation statistics. The arithmetic mean sample (M), the standard deviation (δ), and the error of the arithmetic mean (m) were determined. Significance of differences was assessed by Student's *t*-test. The relationship of quantitative characteristics was studied by the method of correlation analysis. The significance of the linear (Pearson) and rank (Spearman) correlation coefficients was tested using Student's *t*-test [31], [32]. To quantify the tightness of the connection, the correlation coefficient *r* was used, which is calculated in Excel using the f_x function, further statistical functions, the CORREL function.

Results

Overt clinical manifestations of any pulmonary disease were not detected in any of the cases at the time of the examination. Percussion and auscultatory signs of lung injury were scarce during an objective examination and were observed in 20.23% of patients. Shortening of percussion sound was detected in patients of DM1 group (4.05%), DM2 group (6.98%), and DM2CHD group (9.25%). Pulmonary sound was boxy and the nature of auscultatory changes in the lungs was mainly reduced to an extended expiration over the lower lobe of the right lung and was detected in 29.48% of cases. In 13.87%, vesicular breathing with prolonged exhalation was heard, and in 3.47% – weakened vesicular breathing. Fluorography of the chest revealed no changes in all groups. To assess the state of the bronchopulmonary system, a standard X-ray of the chest was performed in two projections.

Table 1: The frequency of the main radiological changes in the lungs in patients with diabetes mellitus (M ± m), %

X-ray index	DM1 (n = 120)	DM2 (n = 175)	DM2CHD (n = 100)
Changing the structure of the lungs roots	38,240±8,330	30.680 ± 4.900	37.000 ± 1.900
Increased transparency of lung fields	26.470 ± 7.500	28.140 ± 4.600**	25.000 ± 2.100
Strengthening of the lung pattern	20.590 ± 6.900	33.300 ± 6.600*	31.000 ± 2.800*
Pleural moorings	-	10.61 ± 5.5	11.000 ± 1.500
Discoid atelectasis	-	-	2.000 ± 1.400
Interstitial changes	8.820 ± 4.800	22.220 ± 6.800**	13.000 ± 1.700***
Bulging of the arch of the pulmonary artery	4.2 ± 0.600	6.820 ± 2.600	7.000 ± 2.300
Hypertrophy of the right ventricle of the heart	-	19.610 ± 5.500	17.000 ± 1.600
Hypertrophy of the left ventricle of the heart	-	69.6100 ± 5.500	87.000 ± 2.800

p: Significance in comparison with the groups DM1, DM2, and DM2CHD: *p < 0.05, **p < 0.01, and ***p < 0.001. DM: Diabetes mellitus, DM2: Type 2 diabetes mellitus, CHD: Coronary heart disease

As can be seen from Table 1, pathological changes occurred in all groups on radiographs. Thus, in the DM1 group, radiographs revealed changes in the structure of the roots of the lungs in 38.24% ± 8.33% of cases, combined with increased transparency of the lung fields in 26.47% ± 7.5% of cases. Strengthening of the lung pattern was detected in 20.59% ± 6.9% of cases and changes in interstitial tissue – in 8.82% ± 4.8% of case. However, the revealed changes are non-specific and coincide with the data that changes in the roots of the lungs and increased lung pattern due to the interstitial component are a non-specific reaction of both the respiratory section and the bronchi to one or another pathological factor.

In patients with DM2, changes in the lung tissue were characterized by changes in the roots of the lungs in 30.68% ± 4.9% of cases, accompanied by increased transparency of the lung tissue in 28.14% ± 4.67% of cases. Strengthening of the pulmonary pattern was detected in 33.3% ± 6.6% of cases, interstitial changes – in 22.22% ± 6.8% of cases, and bulging of the arch of the pulmonary artery – in 6.82% ± 2.6% of cases. Pleural stitches, indicating a history of acute pneumonia, were detected in 10 patients.

X-ray changes in the lungs were detected in almost 49.0% of patients of DM2CHD group and require the nature of diffuse pneumosclerosis. Changes in the roots of the lungs and extensive lung fields were detected in 25.0% ± 2.1% of patients, interstitial changes – in 13.0% ± 1.7%, suspicions of a pulmonary pattern – in 31.0% ± 2.8%, and arch bulging pulmonary increase in blood pressure with hypertrophy of the right ventricle – in 87.0% ± 2.8%. Pleural moorings, identified in 11 patients, testified to a history of acute pneumonia. Small inflammatory foci and discoid atelectasis in the affected parts of the lungs were found in 2.0% ± 1.4% of cases, more often in the right and they occur as hypoventilation.

The results of clinical and radiological studies indicate the existence of a relationship between DM and the bronchopulmonary system. If, the frequency of the detected changes was almost the same in all groups in the physical picture, then the X-ray examination

revealed the greatest changes in the group of diabetic patients (the presence of pleural commissures, discoid atelectasis, bulging of the pulmonary artery arch, and hypertrophy of the right ventricle of the heart). The greatest changes were obtained in patients with pathology of the cardiovascular system and thyroid gland when comparing the results in the group of diabetic patients. Thus, an increase in the pulmonary pattern occurred 2.1 times more often, interstitial changes were detected 4.51 times more, bulging of the pulmonary artery, which is a manifestation of pulmonary hypertension, was registered in 6.82% of cases.

Evaluation of pulmonary ventilation in patients with DM

Changes in the parameters of external respiration, characteristic of impaired pulmonary ventilation, were revealed in the analysis of the state of the function of external respiration (RF) in DM patients with pathology of the cardiovascular system. According to the few data available in the literature, there is a definite relationship between the severity of the course of the pathological process in DM and changes in individual parameters of RF.

In this work, an attempt to comprehensively study the possibility of diagnosing ventilation disorders using X-ray, endoscopic methods, and the study of RF to identify the frequency and severity of these disorders in patients with DM, depending on the complication and stage of the disease was made.

Table 2 shows the indicators of the reliability of differences according to the Student's criterion and assessed the functions of external respiration in patients with DM, (M±m) [31], [32], in the analysis of which, in patients with DM1 and DM2 groups, the static data of pulmonary volumes and capacities were lower than the control group C1 and C2, whereas vital and forced The lung capacities of the DM2CHD group were 1.1 times smaller compared to the DM2 group. The study of the speeds of passage of the air flow through the bronchial tree made it possible to state that in patients of DM1 and DM2 groups, the 1 s FEV decreased by 4.56% and the Tiffno index – by 8.98%. More significant deviations were revealed in the study of MVV indicators, reflecting the state of patency of the proximal and distal parts of the bronchial tree. This concerned the decrease in maximum expiratory velocities with lung volumes equal to 25% and 50% FVC by 10.62% and 8.76%, respectively ($p > 0.05$).

Thus, in patients with DM1 of the DM group, there was a tendency to a decrease in the volumetric velocities of PVV of the air flow throughout the bronchial tree, more noticeable at the level of the predominantly central respiratory tract, which poses a threat of developing chronic diffuse lung diseases. The results obtained confirm the literature data [33], [34]. Analysis of the state of RF in patients of DM2 group indicates more expressed disorders of pulmonary ventilation.

RF disturbances were registered in 23% of 175 patients. Thus, the speed indicators of the passage of the air flow through the bronchial tree were significantly ($p < 0.01$) reduced: The Tiffno index was 79.13% ± 1.84% versus 96.45% ± 3.52% in the control group ($p < 0.001$). Violation of bronchial patency mainly of the central airways is confirmed by a more pronounced decrease in MVV_{50} (92.6% ± 9.57%) and peak volume velocity to 91.61% ± 4.1% ($p < 0.05$).

Changes in pulmonary ventilation can be obstructive in nature, which is based on a violation of the airway or restrictive in nature in the presence of obstacles to the normal expansion of the lungs during inspiration. The mechanisms of airway obstruction are associated with edematous and inflammatory changes in the bronchial tree, tracheobronchial dyskinesia, and latent bronchospasm in the absence of a clinical picture

Table 2: Indicators of the function of external respiration in patients with diabetes mellitus (M ± m)

Index	Group of patients with DM					Control group		Comparison group	
	DM1 (n = 120)	DM2 (n = 175)		DM2CHD (n = 100)		C1 (n = 20)	C2 (n = 20)	CCHD (n = 20)	Co (n = 20)
		DM2n (n = 3)	DM2o (n = 139)	DM2CHDn (n = 2)	DM2CHDo (n = 76)				
1	2	3	4	5	6	7	8	9	10
VC, l	5,230 ± 0.100	4.740 ± 0.140	4.770 ± 0.170	4.210 ± 0.150	4.070 ± 0.120	5.630 ± 0.160	5.650 ± 0.180	4.820 ± 0.150	5.590 ± 0.170
VC, %	98.420 ± 1.910	95.280 ± 2.370	92.140 ± 2.370	89.540 ± 2.320*	82.630 ± 2.320*	99.960 ± 3.710	99.850 ± 3.710	98.610 ± 3.710	86.960 ± 3.710
FVC, l	5.220 ± 0.110	5.210 ± 0.120	4.590 ± 0.130	4.670 ± 0.140	3.970 ± 0.150	5.500 ± 0.240	5.480 ± 0.230	4.980 ± 0.230	5.480 ± 0.230
FVC, %	98.350 ± 2.100	96.840 ± 1.400	83.320 ± 1.400	86.320 ± 2.610***	79.520 ± 2.610***	100.130 ± 2.790	100.080 ± 2.790	100.060 ± 2.790	98.340 ± 2.790
FEV_1, l	4.120 ± 0.100*	4.020 ± 0.130	3.470 ± 0.130	3.380 ± 0.120	3.010 ± 0.120	5.460 ± 0.380	5.420 ± 0.380	5.390 ± 0.380	5.260 ± 0.380
FEV_1, %	94.650 ± 1.600	87.440 ± 2.430*	87.440 ± 2.430*	77.920 ± 2.880*	77.920 ± 2.880*	100.180 ± 3.070	100.410 ± 3.070	100.240 ± 3.070	97.040 ± 3.070
FEV_1/VC	0.790 ± 0.009*	0.850 ± 0.020	0.730 ± 0.010	0.800 ± 0.020	0.720 ± 0.010	0.970 ± 0.030	0.960 ± 0.030	1.120 ± 0.050	0.940 ± 0.040
FEV_1/VC, %	0.960 ± 0.040	0.920 ± 0.030	0.950 ± 0.040	0.870 ± 0.040	0.940 ± 0.040	1.002 ± 0.050	1.005 ± 0.050	1.118 ± 0.050	1.032 ± 0.040
FEV_1/FVC	0.790 ± 0.020*	0.770 ± 0.020	0.760 ± 0.030	0.720 ± 0.020	0.760 ± 0.030	0.990 ± 0.040	0.990 ± 0.050	1.080 ± 0.050	0.960 ± 0.040
FEV_1/FVC, %	0.950 ± 0.010	0.880 ± 0.040	1.010 ± 0.040	0.903 ± 0.020	0.980 ± 0.040	0.980 ± 0.030	0.990 ± 0.050	0.970 ± 0.030	0.980 ± 0.040
PVV, l/s	8.320 ± 0.280	7.850 ± 0.240	7.120 ± 0.240	6.320 ± 0.310	5.940 ± 0.310	8.850 ± 0.660	8.890 ± 0.660	8.860 ± 0.660	8.650 ± 0.660
PVV, %	84.69 ± 3.020*	81.370 ± 2.300	81.370 ± 2.300	66.210 ± 3.270***	66.210 ± 3.270***	96.540 ± 4.110	96.540 ± 4.110	96.540 ± 4.110	96.540 ± 4.110
MVV25, l/s	7.900 ± 0.220	6.970 ± 0.210	6.110 ± 0.210	5.120 ± 0.280	4.790 ± 0.280	8.110 ± 0.310	8.080 ± 0.310	8.060 ± 0.3100.31	8.050 ± 0.310
MVV25, %	91.270 ± 2.470*	87.530 ± 2.480***	77.620 ± 2.480***	68.870 ± 3.570***	61.960 ± 3.570***	99.850 ± 4.730	99.790 ± 4.730	99.810 ± 4.730	95.750 ± 4.730
MVV_{50}, l/s	5.350 ± 0.180	4.650 ± 0.180	4.180 ± 0.180	3.560 ± 0.190	3.250 ± 0.190	5.430 ± 0.370	5.320 ± 0.370	5.400 ± 0.370	5.360 ± 0.370
MVV_{50}, %	96.310 ± 2.170*	86.660 ± 3.130***	82.940 ± 3.130***	69.730 ± 3.260***	59.850 ± 3.260***	99.870 ± 3.220	99.950 ± 3.220	99.870 ± 3.220	97.910 ± 3.220
MVV_{75}, l/s	2.560 ± 0.160	2.320 ± 0.100	2.010 ± 0.100	1.740 ± 0.080	1.390 ± 0.080	2.910 ± 0.120	2.880 ± 0.120	2.860 ± 0.120	2.780 ± 0.120
MVV_{75}, %	97.660 ± 3.510	93.710 ± 3.010*	85.650 ± 3.010*	68.770 ± 3.030***	57.930 ± 3.030***	99.220 ± 3.090	99.490 ± 3.090	99.340 ± 3.090	96.030 ± 3.090
1	2	3	4	5	6	7	8	9	10
AVV_{25-75}, l/s	4.570 ± 0.100	4.320 ± 0.160	4.240 ± 0.160	2.980 ± 0.140	2.720 ± 0.140	5.120 ± 0.250	5.070 ± 0.250	5.010 ± 0.250	5.030 ± 0.250
AVV_{25-75}, %	93.270 ± 1.640	88.220 ± 2.180**	82.200 ± 2.180**	71.740 ± 2.970***	60.250 ± 2.970***	99.970 ± 2.590	99.970 ± 2.590	99.140 ± 2.590	97.970 ± 2.590

*p < 0.05 in comparison with similar indicators in the control Group C1, ***P < 0.001, **p < 0.01, and *p < 0.05 compared to C2 group, $^{+++}$p < 0.001, $^{++}$p < 0.01, and $^{+}$p < 0.05 compared to CCHD group, $^{\&\&\&}$p < 0.001, $^{\&\&}$p < 0.01, and $^{\&}$p < 0.05 versus Co group. DM: Diabetes mellitus, DM2: Type 2 diabetes mellitus, CHD: Coronary heart disease, FEV_1: Forced expiratory volume in 1 s, VC: Vital capacity, FVC: Forced VC, MVV: Maximum volumetric velocity, AVV: Average expiratory volume velocity, PVV: Peak volumetric velocity.

of lung damage. The revealed changes in our studies indicate a change in pulmonary ventilation, mainly of an obstructive type.

The reaction of the bronchi to bronchospasmolytic drugs (anticholinergics and sympathomimetics) was studied to determine the significance of dynamic airway obstruction. The results of the test with Berotek revealed a decrease in the proportion of bronchospasm in the mechanism of airway obstruction, depending on the severity of diabetes. The test with Berotek to detect violations of the mechanics of breathing by increasing the tone of the smooth muscle fibers of the bronchi was positive in 20% of patients with DM2. Various types of ventilation disorders were found in 68% of patients of DM2CHD group during the study of RF at the stage of sub-compensation. Practically, all parameters of RF in patients of this group were reduced in comparison with the control group, and the majority turned out to be significantly reduced. The changes concerned both FEV_1, the Tiffno index, and such speed indicators MVV_{25}, MVV_{50}, MVV_{75}. Thus, a significant decrease in the speed indicators of the passage of air flow through the bronchial tree was obtained: FEV_1 – by 31.64% ($p < 0.05$), Tiffno index – by 39.87% and amounted to 56.58% ± 6.85% ($p < 0.001$), and a decrease in PVV – to 80.0% ± 9.62% at 107.63% ± 4.03% in the control group ($p < 0.05$).

A change in the state of the RF, reflecting the patency of the air flow through the bronchial tree, both in the distal and in the proximal sections, was revealed. This was characterized by a decrease in bronchial patency of the central respiratory tract MVV_{25} (87.2% ± 8.99%) ($p < 0.05$), a decrease in dynamic characteristics at the level of the distal bronchi MVV_{50} and MVV_{75} – 90.2% ± 10.4% and 80.8% ± 9.5% ($p < 0.05$), respectively, with the levels of MVV_{50} and MVV_{75} in the control group – 17.76% ± 4.58% and 105.95% ± 5.22%.

Fibrobronchoscopic characteristics of the condition of the bronchial mucosa in patients with DM

Endoscopic method of research has been increasingly used in the examination of the bronchopulmonary system in recent years. Using this method, it is possible to clarify the diagnosis and determine changes in the bronchial mucosa, the severity and phase of the process, in addition, it is of great importance for the differential diagnosis.

The possibilities of the method were especially expanded when using bronchofibroscopes with fiberglass optics, which made it possible to significantly expand the area of examination of the bronchial tree.

Endoscopic examination of patients of DM1 group revealed two main forms of chronic endobronchitis: Catarrhal endobronchitis (13.53%) and atrophic endobronchitis (3.2%).

Tracheal mucosa of pale pink color, with an expressed cartilaginous pattern, was detected in 34 patients with DM1 during endoscopic examination. The expansion of the ducts of the bronchial glands was noted mainly on the posteromedial walls of the main bronchi with transverse striation of the lobar bronchi. Changes in the form of hyperemia and swelling of the mucous membrane were recorded in 12.41% of patients.

The mucosa of the trachea was pale pink, edematous, easily vulnerable in 23.33% of 175 patients with DM2 on examination. The mucous membrane of the main bronchi up to the mouths of the subsegmental bronchi and beyond was edematous, easily vulnerable, with areas of accumulation of mucous secretions. More pronounced changes were obtained in patients of DM2CHD group. Along with catarrhal endobronchitis detected in 19.22% of patients, changes in the bronchial mucosa according to the type of atrophic endobronchitis were detected in 2.5% of patients. The mucous membrane of the main and intermediate mouths of the lobar and spurs of the segmental bronchi was heterogeneous, areas of pink color changed to pale. At the same time, the mucosa was thinned, the vascular pattern was blurred, the folding was smoothed out, and the cartilaginous relief was somewhat enhanced.

X-ray changes were detected in 43.18% ± 5.28% of patients with DM2 group with scarcity of physical data. Indicators of the function of external respiration indicated a violation of patency at the level of the distal bronchi. Thus, a decrease in the indicators of the Tiffno index by 17.32%, MVV_{50} and MVV_{75} – by 25.16% and 7.55%, respectively, was revealed, the PVV decreased by 16.02%. The results of a positive test with Berotek were regarded as broncho-obstructive syndrome in 45.2% of patients, and changes on endoscopy regarded as catarrhal endobronchitis in 21.31%, which indicated changes in the parameters of the passage of air flow through the bronchial tree.

Significant changes were revealed in physical and radiological pictures in the lungs in patients of DM2CHD group (29.48% and 50%, respectively). Changes in the RF parameters were characterized by a decrease in the speed indicators of the passage of air flow through the bronchial tree: FEV_1 – by 31.64%, Tiffno index – by 39.87%, a decrease in PVV – by 27.63%, as well as indicators of bronchial patency as central MVV_{25}, so distal bronchi MVV_{50} and MVV_{75}. The results of a positive test with Berotek in 20% of patients with DM2 in the group with an obstructive type of pulmonary ventilation disorders, indicating a decrease in the significance of the bronchial reactivity component, along with catarrhal endobronchitis, detected in 13.5% of patients with DM1 and atrophic endobronchitis (3.2%) characterize the progression of ventilation disorders.

Pathological disorders of the lungs in patients with DM

In addition to the fact that the myocardium of patients (nine men and eight women) was examined, the lungs were also examined. Histological changes in 4 (23.5%) patients with DM1 were stereotyped and were characterized by alveolitis, septoalveolar fibrosis, and the formation of «microcystic lung» areas. In the arterial vessels of the pulmonary circulation, there were changes of Grade I in the form of copper hypertrophy, changes of Grade II with ring shaped or eccentric formation of the intimal muscle layer, which were sometimes combined with severe hyperelastosis and sclerosis (changes of Grade III) (Figure 1).

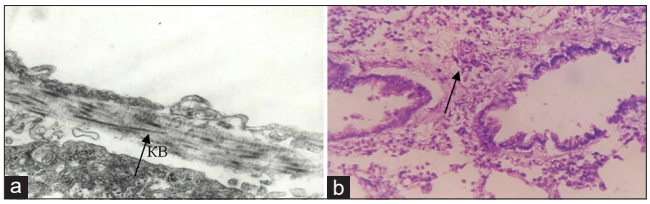

Figure 1: Pathomorphology of the lungs in patients with diabetes mellitus (DM). (a) (DM1) Sclerosis of the wall of the interalveolar capillary. Electrongram. Magnification: ×12,200. (b) DM2 – diffuse fibrosis of the bronchial wall. Peribronchial pneumofibrosis. Staining: H and E, ×200

Pre-capillary arterioles, with pronounced hyperplasia of smooth muscles in the wall and a significant narrowing of the lumen, occurred. These changes were common, but were especially expressed in the muscular arteries of the intralobular bronchi and terminal bronchioles and in the arterioles of the respiratory bronchioles and alveolar passages. In the venous parts of the pulmonary circulation, up to the venules, in some vessels, there was hypertrophy of muscle tissue with the formation of a clear muscle membrane, in others – a sharp hypertrophy, sclerosis, and sometimes hyalinosis of the intima of the veins with an expressed narrowing of their lumen. There were small veins with tortuosity and almost complete obliteration of the lumen by hyalinized connective tissue, in which individual leukocytes were immured. Occasionally, infiltration of the intima of the veins with mononuclear cells and focal productive phlebitis and venulitis was observed.

Hemodynamic changes in the vessels of the lungs in patients with DM2 (5%–24.9%) were of a widespread systematic nature. There were muscular arteries with a narrowed lumen due to neoplasm of the intimal muscle layer, thickening, and hyperelastosis of the middle membrane. In places, an expressed narrowing of the lumen of the arterioles and degenerative changes in the internal elastic membrane with the formation of lumps and grains were observed. The elastic membrane was thick and split in small and medium arteries. Hyperelastosis, hypertrophy of muscle tissue, narrowing of the lumen, and thickening of the intima were noted in small veins and venules, usually due to the neoformation of longitudinal smooth muscles, sometimes due to sclerosis and hyalinosis of the walls.

In some interlobular veins, phenomena of focal productive endophlebitis were found with focal thickening of the intima and accumulation of lymphocytes and macrophages in them. The contours of the capillaries were clearly identified due to the thickening and fuchsinophilia of the basement membranes. As damage and fibrosis of the alveolar tissue increase, hypoxic processes progress in it, type I pneumocytes are not formed, and, consequently, the function of the air-blood barrier is impaired. It was the activation of fibroblasts that led to an increase in septal fibrosis in the lungs. Progressive septoalveolar fibrosis leads to the development of hypertension of the pulmonary circulation and the corresponding restructuring of the pulmonary vessels. An alveolar-capillary block, severe fibrosis, and a microcystic lung developed.

Atherosclerosis indices were detected in 8 (47%) patients of the DM2 with CHD group during macroscopic examination of the trunk and large branches of the pulmonary artery. Dystrophic changes and necrosis of the endothelium with subsequent desquamation were detected by microscopic examination in the pulmonary artery and its branches, including arterioles. These changes may be related to metabolic changes. Violation of the protective function of the endothelium creates favorable conditions for the penetration of plasma proteins into the vascular wall (as is known, the lungs are organs with relatively low vascular permeability), which led to edema and plasma impregnation of the walls of small branches of the pulmonary artery. Loosening of all membranes of the wall of the pulmonary artery and its branches, noted in almost all cases, is associated with the accumulation of protein permeability factor in the serum of patients. The destruction of elastic fibers, in turn, disrupted the barrier function of the arterial wall. The changes revealed in the membranes of the large caliber arteries are the outcome of the disorganization of the connective tissue and hypoxia due to impaired blood circulation in the wall due to changes in the feeding arteries.

Expressed sclerotic changes were noted in the arteries of medium and small caliber and in arterioles along with the disorganization of the connective tissue. Damage to the endothelium and disorganization of the connective tissue contributed to hemorrhage. Plasma impregnation of the walls of small arteries and arterioles was noted in 15 (88.23%) of 17 cases, coagulation, thickening of plasma proteins and hyalinosis – in 3 (17.6%), and sclerosis of their walls – in 10 (58.8%) patients with DM2 with CHD.

Table 3: Morphometric parameters of the lungs in patients with diabetes mellitus (sectional material) (M ± m)

Group	Vessel diameter, mkm	Wall thickness, mkm	Kernogan index, %
DM1 (n = 3)	87,600 ± 2.400	31.300 ± 1.250	35.700 ± 0.430
DM2 (n = 6)	80.200 ± 1.600	31.900 ± 1.510	38.600 ± 0.450
DM2CHD (n = 8)	74.400 ± 1.300*	35.400 ± 1.340*	39.500 ± 0.320
CHD (n = 5)	139.000 ± 3.100	9.500 ± 1.100	6.800 ± 0.210

p – Significance with the comparison group. *p < 0.05. DM: Diabetes mellitus, DM2: Type 2 diabetes mellitus, CHD: Coronary heart disease.

Morphometric study of the lungs of patients with DM

Morphometric analysis was carried out in nine men and eight women who died, the average age was 67.4.5 ± 2.4 years. The cause of death was mainly associated with complications of atherosclerotic lesions of the coronary and cerebral arteries, who had a history of data on the presence of type 1 and type 2 DM (Table 3).

The lungs of people with CHD who did not have DM were taken for comparison. Morphometric analysis of sectional material in patients with DM1 (n = 3) showed a narrowing of the lumen of small branches of the pulmonary artery, an increase in the thickness of the vessel wall due to hypertrophy of the muscle layer, as a result of which the Kernohan index was almost in 4 times higher than that (6.8% ± 0.34%), relative to the lungs of the comparison group, thus indicating a clear increase in resistance to blood flow in the pulmonary circulation (Table 3). Whereas a decrease in vessel diameter and an increase in wall thickness were noted in the DM2 group (n=6), especially in patients with DM2 and CHD (n=8), therefore Kernogan index was in 5.8 times higher than in the control group and 1.1 times higher in DM1 and 1.2 times in DM2. Kernohan index was in 5.8 times higher than in the control group and 1.1 times higher in DM1 and 1.2 times in DM2. The study of small muscular arteries in the lungs showed that in patients with DM2 and CHD with the presence of latent postcapillary arterial hypertension, restructuring of the branches of the pulmonary artery into the vessels of the trailing type was detected. The elastic membranes in them had a tortuous character due to vasoconstriction. The intima was well expressed, the endothelial cells closely adhered to each other, their nuclei were intensely stained and bulged into the lumen of the vessel like a «palisade». In the latter, against the background of a well-developed circulatory muscle layer (indicating the existence of latent arterial pulmonary hypertension), a longitudinal layer of leukocytes appeared, located in the medial internal elastic membrane.

Discussion

Thus, if the physical examination revealed changes in 23.7% of patients with DM1, then X-ray studies revealed changes in 38.72% of patients with DM1 and in 30.68% of patients with DM2, at a combination of DM2 with CHD, radiological changes were detected in 49.0% of patients. Since in chronic diseases against the background of diabetes, the pathological process primarily affects the vessels of the lungs, radiological signs are detected mainly in the interstitial tissue.

The results of the study of RF in 68% of patients of DM2CHD group revealed disorders of various nature and severity. Thus, a restrictive type of disorder was found in 16% of patients, which was characterized by a significant ($p < 0.05$) decrease in VC and corresponded to 3.89 ± 0.14 l versus 5.07 ± 0.6 l in the control group. An obstructive type of pulmonary ventilation disorder was detected in 32% and was characterized by a significant ($p < 0.05$) decrease in capacitance parameters (FEV_1 and Tiffno index). The most profound changes in the lungs reflected the mixed type, diagnosed in 20% of patients, with changes in FVC, FEV_1, and Tiffno index. The Berotek test, carried out in 32% of patients of DM2CHD group with an obstructive type of pulmonary ventilation disorder, was positive in <20% of patients and indicated that sclerotic processes, a decrease in lung elasticity, and a decrease in the significance of the bronchial reactivity component in the pathogenesis of bronchial obstruction were more developed in diabetes.

In the study [35], spirography parameters depended to a greater extent on the state of metabolic control of carbohydrate metabolism in patients with DM2. Obesity, diseases of the cardiovascular system, and the duration of the disease contributed to the violation of bronchial patency. In addition, a 10% decrease in FEV_1 was associated with a 12% increase in all deaths among those examined. The results of studies that have revealed associations between spirography parameters and mortality allow us to consider the deterioration of RF as an independent risk factor for mortality, and the determination of FEV_1 and FVC as indicators of health status [36], including diabetes [37], [38], [39]. It was found that FVC in DM decreases to a greater extent than FEV_1.

Thus, our results indicate the involvement of the bronchopulmonary system in the pathological process in patients with DM. According to the complex examination, changes were detected in 43.93% of patients, including 5.78% of patients with DM1 group, 24.28% of patients with DM2 group, and 62% of patients with DM2CHD group. In patients of DM1 group with minimal physical changes, the RF indicators were characterized by a tendency to impaired patency at the level of predominantly central airways, as evidenced by a decrease in FEV by 4.56% per 1 s, Tiffno index by 8.98%, and changes in MVV_{25} and MVV_{50} by 10.62% and 8.76%, respectively. The obtained data coincided with the changes during bronchoscopy, which revealed non-specific changes in the mucous membrane of the bronchial tree in 29.41%.

Involvement into the pathological process of the bronchopulmonary system is manifested by

a variety of functional and morphological changes that may be of basic importance in the pathogenesis of chronic lung diseases. The analysis showed that the majority of diabetic patients without respiratory diseases had ventilation disorders, predominantly of a mixed nature. The state of RF depends on the indicators of carbohydrate metabolism, the presence and severity of late complications of diabetes, which determine the severity of the disease. Therefore, the identified disorders in the lungs allow us to draw the following conclusions: An increase in pressure in the pulmonary circulation system is naturally accompanied by a compensatory venoarterial reaction, which is characterized by hypertrophy of myocytes in the middle shell of arterioles and narrowing of their lumen. Hemodynamic restructuring of veins and venules in the pulmonary circulation system is characterized by hypertrophy of the muscle layer of the wall, followed by intimal sclerosis, and neoplasm of intimal muscle layers. Even the accumulation of hematogenous cells around the venule is a natural phenomenon in blood flow disorders, in particular, with slowing blood flow and venous hypertension.

The value of the vessels of the trailing type as regulators of blood supply in the pulmonary circulation in conditions of pulmonary hypertension plays an important pathogenetic role. The presence of a longitudinal muscle layer in the vessels of the trailing type makes it possible to completely stop the blood flow in one or another part of the microvasculature, and contributes to a change in its direction.

Conclusions

1. Pathogenetic mechanisms of disorders of the bronchopulmonary system were revealed in 38.4% of patients with DM1. They were manifested by a decrease in the function of external respiration due to the volumetric airflow rates of the predominantly central airways and an increase in bronchial resistance; alveolar hypoventilation of the restrictive type in 23.3% of patients with DM2. It was registered catarrhal endobronchitis in 21.31% of cases and MVV decrease by 50%, peak volume velocity up to 91.61%, and impaired diffusion of gases through the alveolar-capillary membrane
2. Restrictive and obstructive disorders were detected in 62% of patients with DM2CHD, 19.22% of patients had catarrhal endobronchitis, a significant decrease in VC, FVC, capacitive FEV_1, Tiffno index, and impaired ventilation-perfusion ratios and pulmonary blood flow
3. Damage and fibrosis of the alveolar tissue, damage to the endothelium, and disorganization of the connective tissue were revealed at the ultrastructural level in the lungs of patients with DM, which led to hemorrhages and plasma impregnation of the walls of small arteries and arterioles in 15 (88.23%) of 17 cases, to coagulation, thickening plasma proteins, and hyalinosis – in 3 (17.6%) cases and sclerosis of their walls in 10 (58.8%) cases.

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