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RESPIRATORY MUSCLES STATUS CHANGES DURING CHRONIC OBSTRUCTIVE PULMONARY DISEASE PROGRESSION

Summary

This article presents the results of cross-sectional randomized clinical trial for assessing the respiratory muscles status in patients with different stage of chronic obstructive pulmonary disease. The results of ultrasound densitometry were compared with the morphological study of the internal oblique abdominal muscle.

Keywords

Chronic obstructive pulmonary disease, sarcopenia, respiratory muscles, ultrasonic densitometry.

With advancing age, sarcopenia (the loss of muscular mass) becomes one of the processes accompanying it. Sarcopenia is divided into the primary (there are no other reasons of muscular mass decrease) and secondary due to the loss of muscular mass as a result of any disease [20]. The incidence of primary sarcopenia fluctuates from 5% to 13% among persons at the age of 60-70 years [4]. The decrease of muscular mass is not an isolated process because it goes simultaneously with accumulation of fatty mass [23, 34]. There is a tendency to a higher frequency of fatty infiltration occurrence in satellite cells in sarcopenia the consequence of which is the occurrence of fatty muscles infiltration [32].

Currently, more and more attention is given to disorders of skeletal and respiratory muscles (among other extrapulmonary complications) in chronic obstructive pulmonary disease (COPD), which is characterized by their progressing atrophy (with the loss of muscular strength and mass) as well as subsequent formation of physical exercise intolerance and chronic respiratory insufficiency [3, 10, 19]. The latter depends not only on the degree of severity of pulmonary pathology [21, 31] but also on extrapulmonary disorders [18, 30]. The decrease of respiratory muscles (RM) strength by 15-30% in 20-50% of COPD patients (depending on the severity of the disease and kind of RM) was detected [6]. A loss of muscle strength is predominantly the result of RM atrophy and not loss their contractile properties [11]. Besides, it is believed [33] that the function of intercostals and sternocleidomastoid muscles are at less of a disadvantage than the diaphragm in the presence of severe lung hyperinflation. Insufficient RM inspiratory activity leads to hypoventilation occurrence while weakness of expiratory RM favors the development of dynamic hyperinflation which increases during exercise [2, 24, 28]. The increase of RM fatigability and their atrophy are connected (in a complex manner) with occurrence of breathlessness on exertion as well as the exercise limitation.

It was shown [5, 8], that the long presence of bronchial obstruction (which increases the work and oxygen demand of breathing) in COPD leads to RM overburden and reduction of their ability to generate the maximum respiratory effort. RM answer by their hypertrophy in response to increased RM functional load even in initial COPD stages [8]. Then (during the progress of COPD), RM strength decreases on the background of atrophic changes increase. The atrophy of muscles is reversible but only partially in COPD patients [6].

The insidious development of flow limitation and hyperinflation over many years in COPD allows for several structural adaptive mechanisms of muscles to chronic mechanical loading come into play to preserve the functional strength of overburdened RM [13, 15, 27, 35]. They include the reduction in sarcomers length and increase in the relative proportion of fatigue resistant type fibers as well as mitochondrial concentration (which improves oxidative capacity). The presence of differences in morphological changes occurring during the damage of the myofibrils was detected in COPD [29]. Thus one of the most common forms of muscular dystrophy is the formation of contractures when myofilaments become deregulated and displaced whereas myofibrils lose cross-section striation [16]. The reduction of capillaries quantity in unit of the area in muscular tissue in COPD patients was revealed as well [14].

The frequent decrease of body weight in COPD patients is observed with years first of all at the muscles expense while its increase occurs due to accumulation of fatty mass. Fatty muscles infiltration leads to

their decreased strength and inadequate functioning. Indeed, arising hypodynamia, in turn, stimulates the growth of sarcopenia. One more mechanism of the muscular mass decrease is the imbalance (to the side of catabolism) between synthesis and protein degradation. It is caused by the depression of a humoral factors formation which stimulate the protein synthesis with a simultaneous expression of subclinical inflammation factors (TNF-α, IL-6) and depression of the myocytes apoptosis [9, 26].

The role of RM in common muscular status is a little isolated because of the necessity to overcome the elastic properties of chest. The main thing for RM is the peak effort (where type II muscular fibers play a bigger role), whereas the endurance and relative strength have greater importance for the skeletal muscles. Basic characteristic of RM is the airflow peak speed during expiration, but its relationship with sarcopenia is not established to a full extend. Inspiratory RM in COPD patient should generate more negative intrathoracic pressure than normally for adequate alveolar ventilation. It is due to the presence of internal positive pressure at the end of expiration phase as well as static and dynamic hyperinflation [2, 24].

The appearance of RM dysfunction in COPD occurs due to the complex action of some factors [1, 12, 14, 17, 19, 36, 39]: increase of proinflammatory mediators (which plays a key role in the pathogenesis of these changes); decrease of nutritional status and anabolic hormone levels; tissue hypoxia; oxidative stress; reduced capillarity and proportion of type II fibers; muscle apoptosis; use oral or inhaled corticoids in high doses. Besides, RM are involved in this pathological process with some delay [29]. Thus, the increase of circulating proinflammatory cytokines (IL-1, 2, 6; TNF-α, interferon-γ) levels in the bloodflow leads to the decrease of muscular fibers synthesis. Indeed, TNF-α directly or indirectly promotes the development of systemic inflammatory process and proteolysis of myosin as well as the increase of catecholamins synthesis [38]. Besides, in COPD the pathological changes of muscular fibers which are combined with the decrease of oxidative enzymes as well as transverse section area of muscular fibers are formed [25]. These changes of RM decrease the efficacy of muscles mechanical work.

The ultrasonic method allows direct detection of separate structures and early pathological changes in RM of COPD patients and their timely correction afterwords. Unfortunately, only the area of crosssection RM and their amplitude of movement are currently analyzed by this method [37]. At present the estimation of morphometric changes in RM are sparse [7]. The relationship between these RM changes and other pathological processes occurring in COPD has not been studied in detail yet. Usually biopsy of RM (with the subsequent morphological and histochemical analysis) is used only for scientific aims. All this emphasizes the importance of developing new noninvasive dynamic assessment of functional and structural pathologic changes of RM in COPD patients.

The aim was to assess the RM status (dystrophic changes) by ultrasonic scanner and to compare them with the histological data of bioptic muscular material in males with different GOLD stages of COPD.

Materials and methods

We undertook a trial at the pulmonologic department of the 10-th Minsk City Clinic in 2009-2012 years. All participants gave a written informed consent. The study protocol was approved by the Human Studies Committee on research ethics of the Belarusian State Medical University. The inclusion criteria for the study had been established before the trial and were strictly followed. This inclusion criterion was - males of 50-67 years with different severity of COPD having FEV_1 increase <15% during bronchodilatating test. Exclusion criteria included substantial uncontrolled comorbidity.

The following RM were studied: muscles of inspiration - sternocleidomastoid (SCM), scalenus anterior (SA), external intercostals (ExI) and muscles of expiration - abdominal internal oblique (AIO), abdominal external oblique (AEO), rectus abdominis (RA), transversus abdominis (TA) and internal intercostals (InI). We received the following quantitative indices of RM: homogeneity (IH – which characterized the degree of muscle homogeneity), echogenicity (IE - level of shade of the grey scale, most often emerging in the outlined zone), structure density (ISD – which allowed quantitatively to estimate muscles of different size) and standard deviation (SD – one of the parameters which characterized the amplitude histogram) by using ultrasonic scanner HONDA Electronics HS-2000 (the linear counter with 7,5 MHz/50 mm and with a considerable quantity equal 256 shades of grey color that defined a qualitative level of the histogram) to measure the peak of histograms in the B-mode image.

152 COPD patients (aged 51-67 years) with acute exacerbation (increased wheezing, dyspnea, sputum volume or sputum purulence 1 week prior to admission) of varying severity and control group (34 healthy persons of comparable age, sex and smoking status and body mass index - BMI) were examined.

The special emphasis was placed on the history of chronic, progressive symptoms such as dyspnea, cough and wheezing as well as smoking. Most of these patients were current smokers or ex-smokers (stopped smoking at least 12 months before evaluation) and some of them were nonsmokers. The diagnosis of COPD and its severity was based on the GOLD guidelines. Expressiveness of dyspnea in these COPD patients was defined according to the modified questionnaire MRC [22].

These patients were divided into three consecutive groups according to COPD severity which reflected the evolution of disease (Table 1). The first group ($COPD_1$) consisted of 42 patients with mild COPD (median age and duration of disease - 55 and 4 years respectively; FEV_1 – 83%; BMI – 27 kg/m^2; current smokers – 79%). The second, moderate group ($COPD_2$) was formed by 80 patients (median age and

duration of disease 57 and 10 years respectively; FEV_1 – 55%; BMI – 30 kg/m^2; current smokers – 78%). The third, severe group ($COPD_3$) was formed by 30 patients (median age and duration of disease 60 and 13 years respectively; FEV_1 – 33%; BMI – 25 kg/m^2; current smokers – 86%).

As seen from Table 1, the control group according to the median age, percent of patients under 60 years, BMI and intensity of smoking did not differ from $COPD_1$ patients. Compared with normal subjects, $COPD_1$ patients had only decreased ventilation parameters. Thus, $COPD_3$ patients had significantly higher median age, disease duration, MRC index breathlessness and number of present smokers as compared with the control group as well as $COPD_{1,2}$ patients, while BMI was significantly lower than in $COPD_2$. As shown in Table 1, the significant increase in the number of exacerbations (which are the important component of clinical evolution of disease) over the past year was found in severe COPD as compared with mild to moderate COPD.

We detected progressing decrease of ventilation parameters during COPD evolution ($COPD_1 \rightarrow COPD_3$): FVC from 86% to 38% respectively, FEV_1 from 80% to 33% and blood oxygen saturation from 97% to 93% respectively. These patients were treated with a combination of inhaled long active anticholinergic or β_2-agonists, inhaled steroids and antibiotics (if there was the clinical evidence of exacerbation types 1 or 2 according to the criteria of Anthoninsen).

Additionally we did morphological research of biopsy material of AIO in 25 stable $COPD_{1,2}$ patients (Table 2) which was received during herniotomy (inguinal) for estimation of the accuracy of proposed ultrasonic method in the diagnostics of RM dystrophic changes. The histological method of hematoxylin-eosin staining and the latter by Van Gieson were used. We quantitatively estimated the following morphological signs in RM: atrophic and sclerotic changes, myolysis, fragmentations and contractures of myofibrils, the presence of granules in sarcoplasm, proliferation of perimysium cells and fibroblasts as well as growth of fatty tissue into the muscular tissue.

Statistical analysis was performed using the program software Microsoft Office Excel 2010 and the package of applied programs of Statistic 6.1 (USA). The preliminary analysis of the considered variables (for the correspondence to the normal distribution) was made according to the criteria of Shapiro-Wilk. The results of analysis were shown as median and in

Table 1. Baseline characteristics of patients [Me (25, 75)]

Parameters	Control (n=15)	$COPD_1$ (n=42)	$COPD_2$ (n=80)	$COPD_3$ (n=30)
Median age (years): <60/>60 years (%)	56 (54; 59) 73/27	55 (51; 59) 79/21	57 (53; 60)* 66/34	60 (55; 67)*,**,*** 50/50
Body mass index (kg/m^2)	26,0 (23,5; 30)	27,0 (24; 30)	29,7 * (24,8; 33)	25,1 *** (20,8; 32,1)
Present smokers (%)	60	79	78	86*
Smoking history (index pack-years)	17 (10; 30)	20 (10; 30)	20 (10; 30)	28 (15; 40)
Median duration of COPD (years)	-	4 (2; 6)	10 (4; 14)	13**,*** (8; 19)
Number exacerbation for the last year	-	1 (0,1; 2)	2 (1; 3)	3**,*** (2; 4)
MRC index dyspnoea (score)	0	0 (0; 1)	2 (1; 3)	3**,*** (2; 3)
FVC (% pred.)	102 (98; 112)	86 (75; 90)*	55 (48; 66)*,**	38 (28; 46)*,**,***
FEV_1 (% pred)	88 (77; 94)	80 (75; 87)*	55 (50; 64)*,**	33 (22; 40)*,**,***
FEV_1/FVC (%)	98 (89; 104)	70 (66; 71)*	67 (57; 70)*	51 (39; 57)*,**,***
psO_2 (%)	97 (96; 97)	97 (96; 97)	96 (95; 98)	93 (90; 95)*,**,***
C-reactive protein (mg/dl)	0,4 (0,1; 2,0)	0,6 (0,1; 2,8)	3,3 *,** (1; 5,6)	2,9 *,** (0,9; 5,4)
Corticoids (%): inhaled/oral; with inhaled long active anticholinergic	-	-	35/2 20	43/13*** 7
Inhaled long active в$_2$-agonists with inhaled corticoids (%):	-	-	1	17***

- p<0,05 vs the control; ** - p<0,05 vs $COPD_1$; * - p<0,05 vs $COPD_2$*

Table 2. Clinical characteristics of COPD patients who underwent morphologic research [Me (25; 75)]

Parameters	Control (n=11)	$COPD_1$ (n=12)	$COPD_2$ (n=13)	Kruskel-Wallis ANOvA, p
Age, years	55 (48; 60)	56 (51; 60)	57 (56; 59)	>0,05
BMI, kg/m^2	24 (23; 28)	24 (22; 26)	24 (24; 26)	>0,05
FEV_1, %	94 (85; 98)	79 (75; 87)	54 (49; 64)	<0,05*
Present smokers, %	58	68	80	<0,05*
Index “packs/years”	12 (4; 20)	14 (5; 20)	29 (22; 40)	<0,05*

**- p<0,05 - significant difference between these groups*

terquartile range (25-75%) for the parameters which do not obey the normal dispersion. The comparison of the non-parametric parameters in the two independent groups was carried out according to the criterion Mann-Whitney, while in three or more independent groups it was performed with the aid of Kruskel-Wallis rank dispersive analysis. The χ^2 method Fisher's was used for detection of the significant difference between independent groups according to the frequency characteristic of the investigated sign. The Spearmen correlation coefficient (rs) was used to describe the relationship between the two quantitate variables which differed from the normal dispersion. All P values were two tailed. The significance level was set at p<0,05.

Results

The ultrasonic images of RM in the control and in all patients groups were significantly different. Thus, the tissue of the RM was represented by poor echogenic and homogenic structure in the control group. The peak histogram of abdominal external and internal oblique muscles showed that more often detected echogenicity was revealed in the initial part of the grey color scale (Fig. 1). Additionally, the small SD (i.e. a wider spectrum of grey color gradation was involved) value and the narrow basis of this graph denoted the uniformity of this muscular tissue (i.e. more narrow spectrum of grey color gradation was involved).

We detected various ultrasonic images denoting the increase of echogenicity and heterogeneity in muscular tissue of $COPD_{1,2,3}$ patients. The increase of the basis of the peak histogram and value as well as the changes of ISD, IE, IH were observed. Thus, in Fig. 2 you can see the typical amplitude histogram of abdominal oblique muscles in mild to moderate COPD patients.

We determined that the changes of ISD, IE, IH in RM of inspiration varied in a complex way (Table 3; Fig. 3, 4) during COPD progression. Thus, the significant increase of IH, ISD against the background of IE decrease was revealed. So, ISD of SCM was increased significantly in $COPD_1$ (by 9% vs the control) while it was decreased in $COPD_2$ (by 14% vs the control). IE was decreased in $COPD_1$ and increased in $COPD_2$ (both by 18% vs the control). Vice versa IH of SCM increased in $COPD_1$ (by 6% vs the control) and decreased in $COPD_2$ (by 13% vs the control).

We observed the increase of IH of SCM in $COPD_3$ (by 8% vs $COPD_2$; p<0,05), but this parameter still remained below the control. A similar picture was detected in ISD in $COPD_3$: increased ISD vs $COPD_2$ (by 21%; p<0,05) which almost reach the control value. Dynamics of these indices of SA was similar to SCM, but was less pronounced during COPD progression. IH of ExI was decreased significantly in $COPD_{2,3}$ (by 13% and 15% vs the control), while IE of ExI was increased in $COPD_{2,3}$ (by 29% and 21% vs the control). ISD of ExI did not significantly differ from the control value. These phased changes of echogenicity index during developing COPD are quite well evident in Fig. 3.

The changes of echodensitometric parameters of expiration RM were similar to RM of inspiration. So, IH and ISD of AIO were decreased significantly in $COPD_2$ (both by 7% vs the control) and in $COPD_3$ (by 7% and 5%), while IE was increased in $COPD_{2,3}$ (by 14% and 10% vs the control). IH and IE of AEO did not differ from the control in $COPD_{1,2,3,}$ although ISD was decreased only in $COPD_2$ (by 10% vs the control). IH and ISD of RA were also decreased in $COPD_2$ (by 18% and 20%) and $COPD_3$ (by 20% and 13% vs the control) while IE was increased significantly in $COPD_{2,3}$ (by 31% and 42%). The dynamics of SDI changes in RM noticeably differed from the dynamics of IE during COPD progression (Fig. 4).

Additionally we studied the relationship between the patient's physical activity (according to severity of breathlessness) and introduced echodensitometric parameters of RM. All the patients were divided into four subgroups according to the degree of dyspnea expressiveness (scale MRC). In these subgroups significant differences according to IH for AEO; ExI; InI; SCM; SA and RA were revealed. The changes of IE were expressed to a greater extent as compared

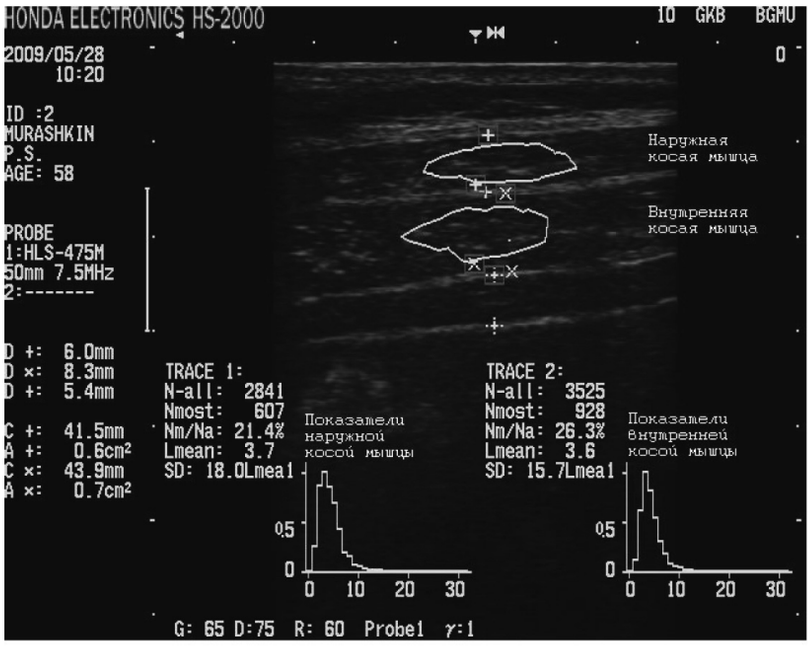

Fig. 1. The ultrasonic image of abdominal muscles [external and internal oblique] without tendon part and their peak histograms in a healthy 58 year old man

IH = N m/N all; IE = L mean (the most often meeting shade of grey color);

ISD= N most /S (where S is square of the interest zone)

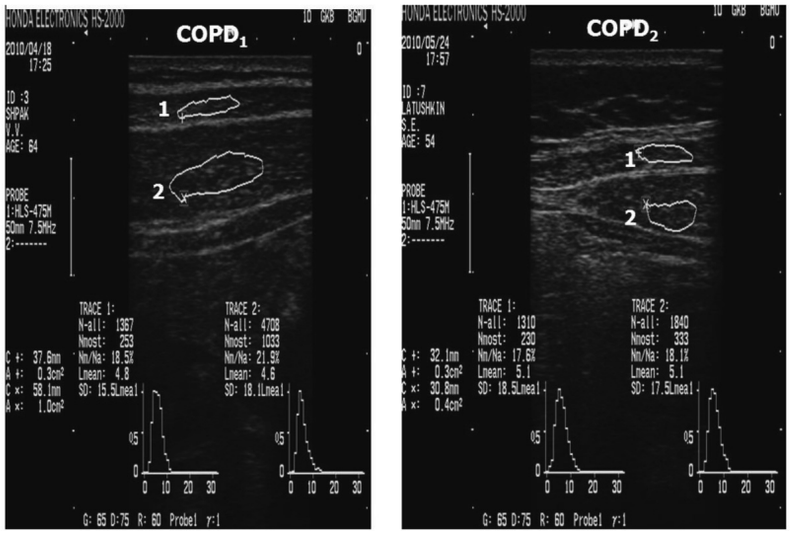

Fig. 2. Echodensitometric data of abdominal muscles external (1) and internal (2) oblique in patients with COPD1,2

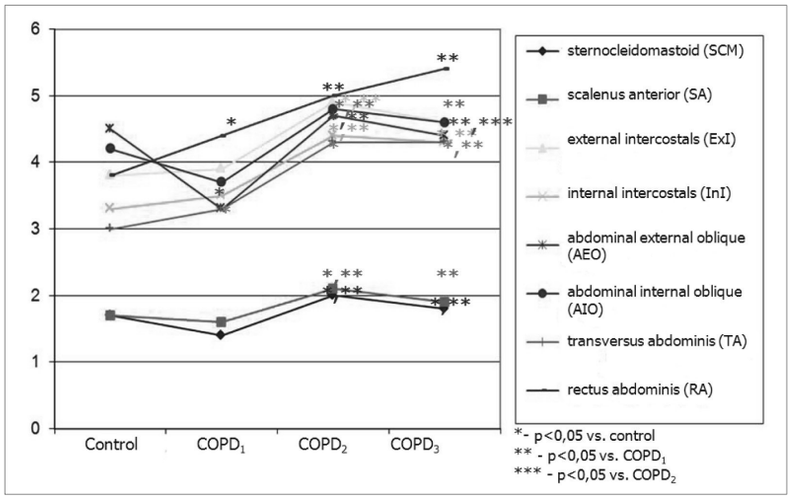

Fig. 3. Dynamics of echogenicity index changes in RM during COPD progression

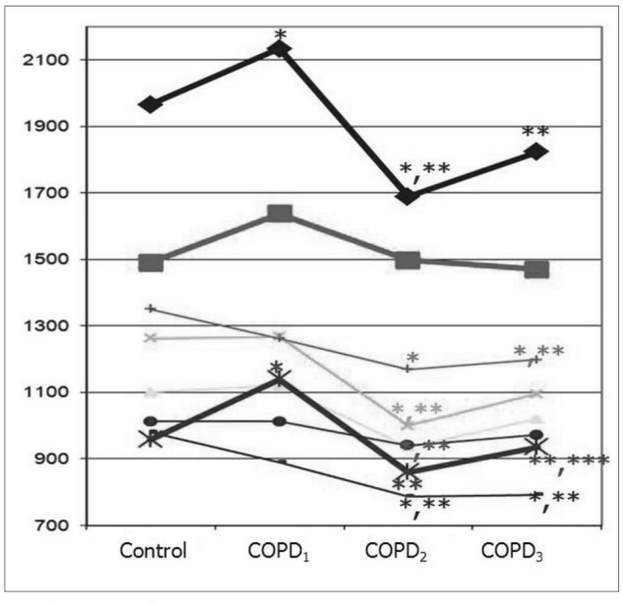

Fig. 4. Dynamics of structure density index changes in RM during COPD progression

with IH in these COPD subgroups. Thus, a significant difference between the subgroup of MRC_0 and subgroups of $MRC_{1,2,3}$ according to IE for all the studied RM was revealed (Table 4).

Morphological research of RM in $COPD_{1,2}$ patients gave the following picture (Table 5). Thus, structural abnormalities - atrophic changes were found in 25% of $COPD_1$ patients as compared with 69% of $COPD_2$ patients and in 45% of persons from the control group (χ^2=4,91; p=0,085). Additionally in $COPD_2$ the share of patients with atrophic changes in muscular tissue as compared with $COPD_1$ (69% and 25% respectively) was increased (χ^2=4,89; p=0,047). It is necessary to note, that this morphological sign was not specific for COPD patients because it was often detected in the control group, too.

As seen in Tab. 5, the presence of myolysis in RM (Fig. 5A) was observed both in $COPD_{1,2}$ (in 92% of these patients), but only in 9% persons from the control group which was less (χ^2=23,6; p=0,00001). In some cases in these COPD patients we detected the presence of myolysis zones in which proliferation of perimysium cells arranged into the continuous series was apparent. Additionally, the presence of granules in sarcoplasm (as the sign of severe dystrophic changes) was revealed. We also observed deeply dystrophic albuminous granules of various sizes among relatively undamaged muscular fibers. The fragmenta tion of myofibrils was present in all observed groups too: 82% in the control, 83% and 85% in $COPD_1$ and $COPD_2$ (χ^2=0,01; p=0,99).

We did not detect the difference between the control and $COPD_{1,2}$ groups according to the presence of perimysium cells proliferation (36%, 67%, 72% respectively; χ^2=2,43; p=0,29) as well as between $COPD_{1,2}$ groups (Fig. 5B). A round-cell infiltrates around microcirculation vessels, perivascular and in intermuscular fatty tissue along the myofibrils but without difference between the control group and $COPD_{1,2}$ patients (χ^2=6,08; p=0,06) were revealed. We observed instill of lymphocytes in separate fibers with fusion of sarcolemma and bordering sarcoplasm in $COPD_{1,2}$ patients but without differences between these groups (χ^2=0,99; p=0,43). We did not detect proliferation of fibroblasts in the control group, but it was observed in 25% and 69% of $COPD_1$ and $COPD_2$ patients respectively. There were differences between the control and these groups (χ^2=13,4; p=0,0012) as well as among $COPD_1$ and $COPD_2$ (χ^2=4,89; p=0,047). Intergrowth of fatty tissue

Table 3. Echodensitometric parameters of respiratory muscles [Me (25; 75)]

Parameters	Control (n=43)	$COPD_1$ (n=42)	$COPD_2$ (n=80)	$COPD_3$ (n=30)
RM of inspiration: Sternocleidomastoid				
IH	41 (30,8; 45,9)	43,4* (38,1; 52,1)	35,7*,** (27,6; 43,4)	38,5** (33; 41,9)
IE	1,7 (1,4; 2,1)	1,4* (1,0; 1,7)	2,0** (1,3; 2,8)	1,8** (1,4; 2,3)
ISD	1965 (1620; 2183)	2133* (1794; 2638)	1688*, ** (1327; 2204)	1823** (1613; 2058)
External intercostals				
IH	24,5 (21,2; 25,1)	23,4 (19,6; 29,1)	21,4*,** (18,8; 24,2)	20,8*,** (16,7; 23,6)
IE	3,8 (3,1; 4,8)	3,9 (3,0; 5,1)	4,9*,** (4,0; 5,6)	4,8*,** (3,4; 5,3)
ISD	1100 (980; 1221)	1120 (940; 1380)	986 (780; 1120)	1020 (816; 1290)
Scalenus anterior				
IH	37,9 (27,8; 45)	38,8 (34,5; 46,6)	33,4*,** (27,2; 40,9)	37,4 (25,4; 45)
IE	1,7 (1,3; 2,5)	1,6 (1,2; 1,9)	2,1*,** (1,4; 3,0)	2,0*** (1,2; 2,9)
ISD	1490 (1175; 1975)	1637 (1280; 2180)	1497 (1105; 2065)	1470 (1190; 1770)
RM of expiration: Abdominal external oblique				
IH	19,1 (16,1; 28,6)	22,9 (18,8; 27,9)	18,0 (15,7; 20,4)	19,2 (16,7; 22,3)
IE	4,5 (2,6; 5,4)	3,8 (2,5; 4,2)	4,7 (4,1; 5,9)	4,4 (3,7; 5,3)
ISD	958 (805; 1331)	1139 (901; 1400)	860*,** (722; 976)	936 (821; 1032)
Rectus abdominis				
IH	19,6 (15,6; 25,1)	18,4 (14,8 26,8)	16,1*,** (13,6; 19,0)	15,7*,** (14,5; 17,9)
IE	3,8 (2,9; 4,8)	4,4 (2,6; 5,2)	5,0*,** (4,0; 6,3)	5,4*,** (4,3; 5,9)
ISD	981 (778; 1221)	890 (761; 1180)	787*,** (669; 917)	792*,** (716; 897)
Internal intercostals				
IH	30,1 (23; 31)	27,8 (23,7; 30,9)	24,4*,** (20,5; 29,4)	24,5*,** (20,4; 27,3)
IE	3,3 (2,5; 4,5)	3,5 (2,8; 4,6)	4,4*,** (3,7; 5,4)	4,3*,** (3,3; 5,8)
ISD	1262 (1015; 1403)	1267 (930; 1555)	1000*,** (770; 1310)	1095 (910; 1380)
Abdominal internal oblique				
IH	20,9(18,2; 27,5)	20,9 (18,3; 23,3)	19,3*,** (17,4; 22)	19,3*,** (17,3; 22,7)
IE	4,2 (3,0; 5,4)	3,7 (3,4; 4,7)	4,8*,** (4,1; 5,8)	4,6** (3,7; 5,5)
ISD	1013 (893; 1325)	1012 (872; 1195)	941*,** (836; 1085)	972 (826; 1171)
Transversus abdominis				
IH	29,5 (26,5; 36,4)	26,7 (22,3; 33,3)	24,0*,** (18,9; 27,6)	25,1* (20,8; 29,6)
IE	3,0 (2,5;3,7)	3,3 (2,6;4,2)	4,3*,** (3,4;5,2)	4,3*,** (3,5;4,7)
ISD	1350 (1163;1695)	1263 (1015;1660)	1170* (937;1335)	1179* (1013;1395)

- p<0,05 vs the control; ** - p<0,05 vs $COPD_1$; * - p<0,05 vs $COPD_2$*

Table 4. The comparison of echogenicity index values in RM with the severity of dyspnea [Me (25; 75)]

RM	MRC_0 (n=26)	MRC_1 (n=20)	MRC_2 (n=83)	MRC_3 (n=24)
AEO	3,0 (2,1; 3,5)	4,3* (3,0; 5,3)	4,7*,** (4,1; 5,6)	4,3*,▯(3,6; 5,6)
AIO	3,5 (3,3; 4,5)	4,2 (3,6; 5,2)	4,8*,** (4,1; 5,8)	4,8*,** (3,6; 5,5)
TA	3,2 (2,4; 3,7)	3,7 (2,7; 4,7)	4,3* (3,4; 5,1)	4,1* (3,4; 4,7)
ExI	3,8 (2,9; 5,2)	4,2 (3,5;5,2)	4,8* (3,8;5,5)	4,6* (4,0; 5,6)
InI	3,4 (2,4;4,0)	3,9* (3,1; 5,5)	4,4* (3,6; 5,3)	4,2* (3,4; 5,9)
SCM	1,4 (0,9;1,7)	1,5 (1,2;2,5)	1,9* (1,3;2,6)	2,0* (1,6;2,3)
SA	1,4 (1,1; 1,8)	1,9* (1,7; 3,0)	1,9* (1,3; 2,8)	2,3* (1,4; 3,2)
RA	3,4 (2,5; 5,1)	5,1* (4,5; 5,6)	5,3* (4,0; 6,5)	4,9* (4,2; 5,7)

** - p<0,05 vs MRC0; **- p<0,05 vs MRC1; ***- p<0,05 vs MRC2; ▯- p<0,05 vs MRC3*

into the muscular tissue (Fig. 6A) was observed in 25% of $COPD_1$ patients and in 69% of $COPD_2$ patients as well as in 36% of persons from the control group. It shows a nonspecific character of these changes although there was a difference between COPD groups and the control (χ^2=12,3; p=0,002) as well as among $COPD_1$ and $COPD_2$ (χ^2=11,54; p=0,0012). We determined a marked focal growth of fatty tissue between muscular fibers and among the damaged muscular fibers (under consideration as a sign of «a false hypertrophy» of muscular tissue).

Sclerotic changes of muscular tissue of RM was observed in 75% of $COPD_1$ patients and in all $COPD_2$ patients (Fig. 6B, 7A) while only in 9% of healthy subjects. It also indicates no specificity of these changes, although there was a difference among these three groups (χ^2=20,6; p=0,00038) as well as among $COPD_1$ and $COPD_2$ (χ^2=5,16; p=0,039) at combination of the expressed and not significant sclerotic manifestations. An expressed interstitial sclerosis which extended to places on the damaged muscular fibers was revealed.

Contractures of myofibrils (Fig. 7B) were observed in 67% and 85% of $COPD_1$ and $COPD_2$ patients respectively, while these changes were not revealed in the control. There was a significant difference between these COPD groups and the control, although such dif-

Table 5. Distribution of $COPD_{1,2}$ patients according to the presence of some morphological signs in RM (n/%)

Morphological sign	Control (n=11)	$COPD_1$ (n=12)	$COPD_2$(n=13)
Atrophy of myofibrils	5/45	3/25	9/69**
Myolysis	1/9	11/92*	12/92*
Proliferation of perimysium cell	4/36	8/67	8/62
Proliferation of fibroblasts	0	3/25	9/69*,**
Intergrowth of fatty tissue into a muscular tissue	4/36	3/25	9/69**
Sclerotic changes: moderate	1/9	7/58	3/23*
pronounced	0	2/17	10/77*,**
Contractures of myofibrils	0	8/67*	11/85*

**- p<0,05 vs control; **- p<0,05 vs $COPD_1$*

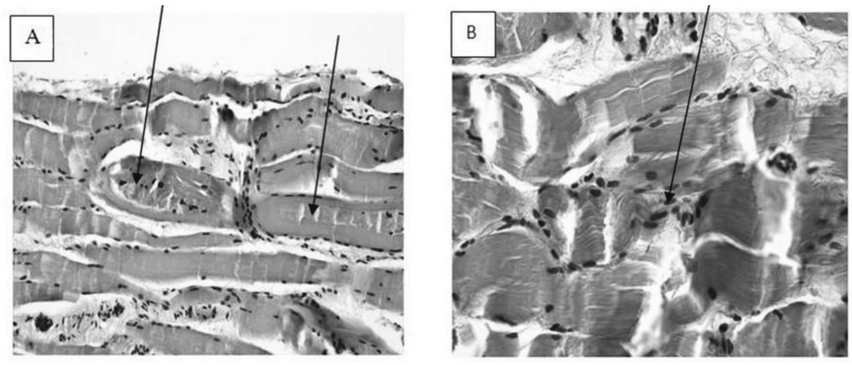

Fig. 5. A - fragmentation and destruction of sarcoplasm in the center of myofibrils and proliferation of perimysium cells and fibroblasts; B - prepresence of contractures in COPD1 patients

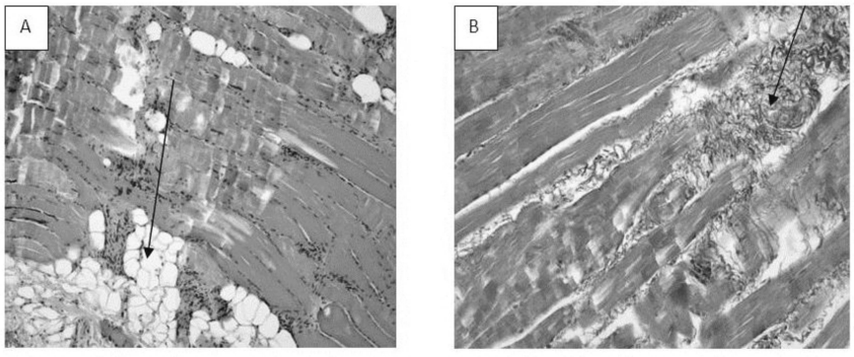

Fig. 6. A - intergrowth of fatty tissue into the muscular tissue and proliferation of peremysium cells; B - the presence of zones with interstitial scleroses and a big number of collagen fibers in COPD1 patients

ference was not detected among these COPD groups (χ^2=1,1; p=0,37). The combination of the presence of interstitial sclerosis around a separate muscular fibers and fascicle as well as of contractures foci was revealed.

The structural changes of accessory RM (which were revealed by ultrasonic densitometry) consisted of echogenicity phased changes (the cause of which may be multifactorial). The relationship between the severity of COPD and dystrophic changes in RM according to the data of ultrasonic densitometry was established. We illustrate this assumption by Fig. 8.

We determined that changes of the echodensitometry parameters in isolated RM were interconnected with the decrease of FEV_1 and with the increase of breathlessness expressiveness in COPD patients. As a pattern of the correlation between the echodensitometric parameter of external intercostals muscle and FEV_1 as well as breathlessness we give the following figures (Fig. 9, 10). Additionally the parallel increase of dyspnoea severity and echogenicity of isolated RM in the course of COPD evolution was detected on the background of decreasing IH and ISD due to expressive atrophy of muscular fibers as well as expansion of connecting and fatty tissue.

Dynamics of these ultrasonic parameters precisely enough reflects the course of dystrophic process in RM during COPD progressing: from compensatory hypertrophy of RM in response to the increase of RM functional load → to their dystrophy with a phase of replaceable expanding fatty and connecting tissue → up to severe atrophy of RM in severe COPD. So, each of the following severity stages of COPD leads to the rising atrophic and degenerative of RM changes. This fact gives grounds to make a conclusion about relationships between RM structural changes (revealed during their ultrasonic research) and functional changes of respiratory system (manifested by decrease of FEV_1 and increase of dyspnea expressiveness) in severe COPD. The significance of these phased echodensitometric parameters changes in RM is not fully understood. This dynamics of echodensitometric parameters in $COPD_1$ could be explained to a certain degree by the increase of echogenicity due to replaceable and excessive growth of fatty and and excessive growth of fatty and connective tissue. Thus, we determined a significant positive correlation between sclerosis manifestations of RM and their index echogenicity (Fig. 11) in COPD patients.

IH and ISD had a little increase in $COPD_3$ as compared with $COPD_2$ while IE was slightly decreased. We can assume that the development of RM fatigue in severe COPD was caused by some factors (decrease of their mass, sclerotic changes and disappearance of fatty mass) which reduced echogenicity of RM. These morphological changes could be due to the expressed systemic inflammation (first of all) as well as changes of hormonal status and high sensitivity of the patients

who received high doses of glucocorticoids during COPD exacerbation (in a less degree).

The advantages of this ultrasonic method in diagnostics of sclerotic changes, intergrowth of fatty tissue into the muscular tissue as well as its atrophic changes were revealed. This method has provided a major source of information for assessing the structural changes of RM. Probably it was connected with the possibility of ultrasonic method to research the muscle for all its thickness. Thus, these morphological data can suggest that alternate increase and decrease of the ultrasonic parameters could be caused by changes of fatty tissue volume in the muscular tissue in different COPD stages of its evolution.

Morphological research of RM is invasive and awkward and be sides is associated with the possibilities of developing some complications, whereas, the

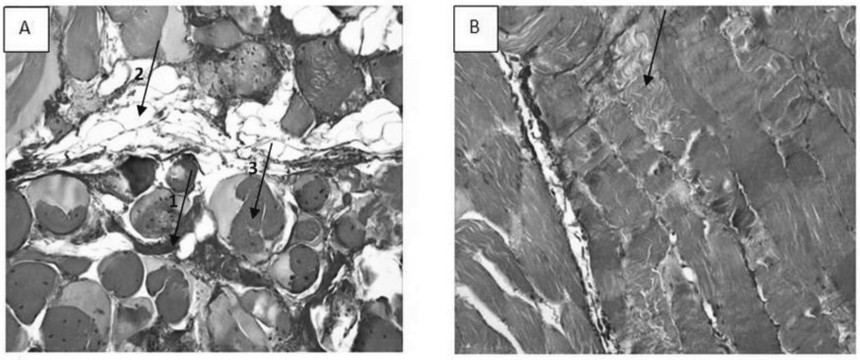

Fig. 7. A - foci of sclerosis in intramuscular regions (1), increase of adipose cells (2) and destruction of myofibrils (3) in COPD2 patient; B - contractures of myofibrils in COPD1 patient

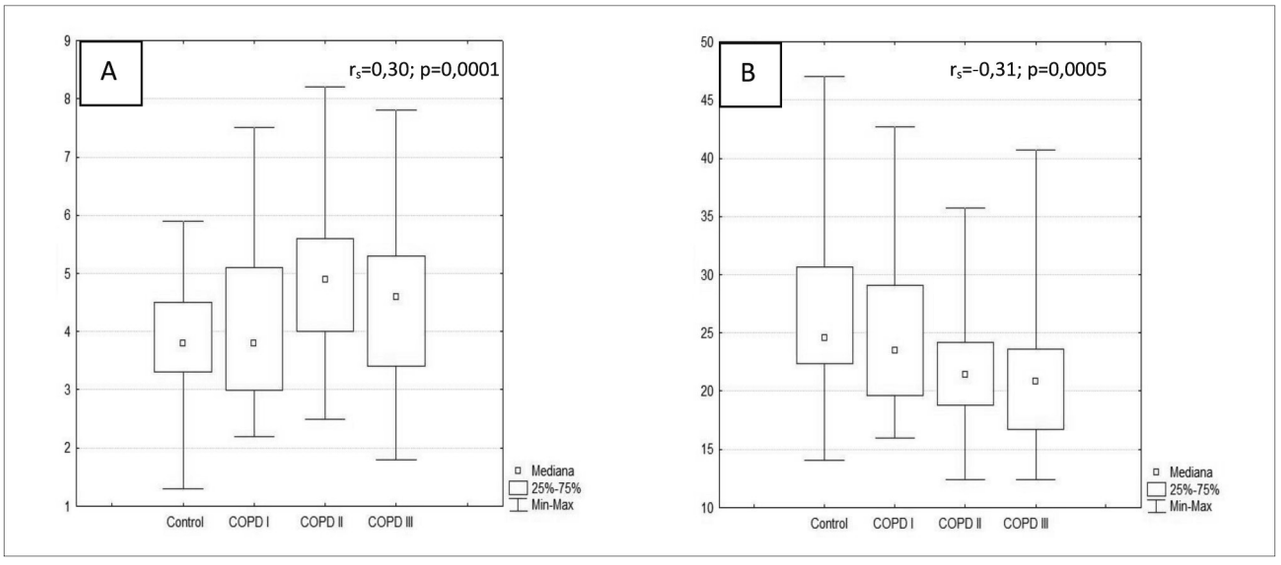

Fig. 8. Relationship between COPD severity and echodensitometry parameters – indices of echogenicity (A) and structure density (B) of external intercostals muscle

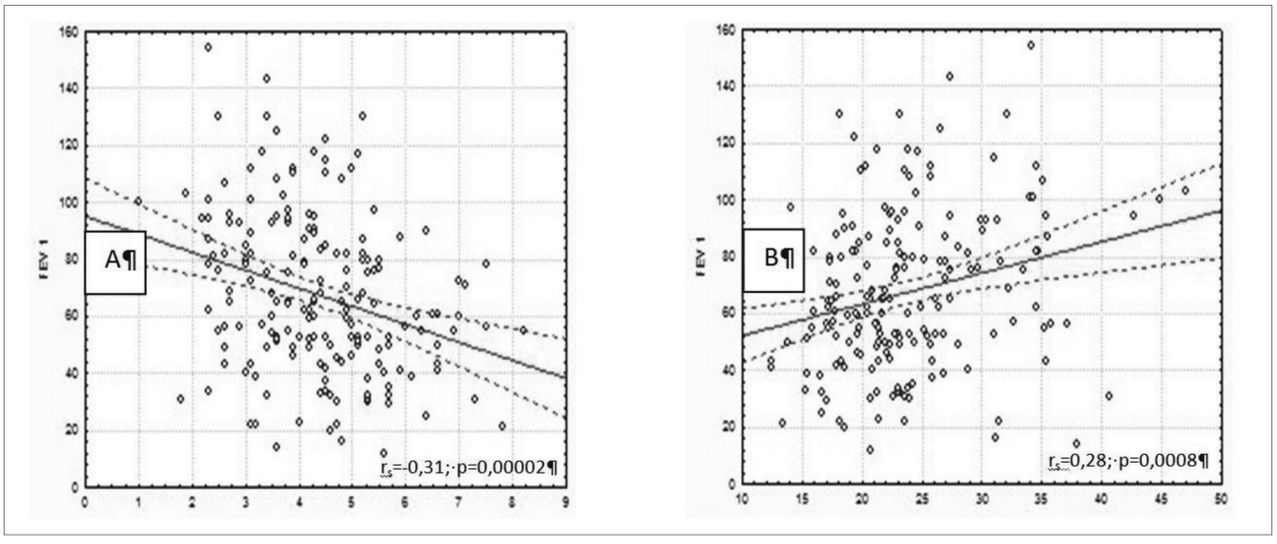

Fig. 9. Correlation between FEV1 and the echodensitometric parameters – indices of echogenicity (A) and homogeneity (B) of external intercostals muscle

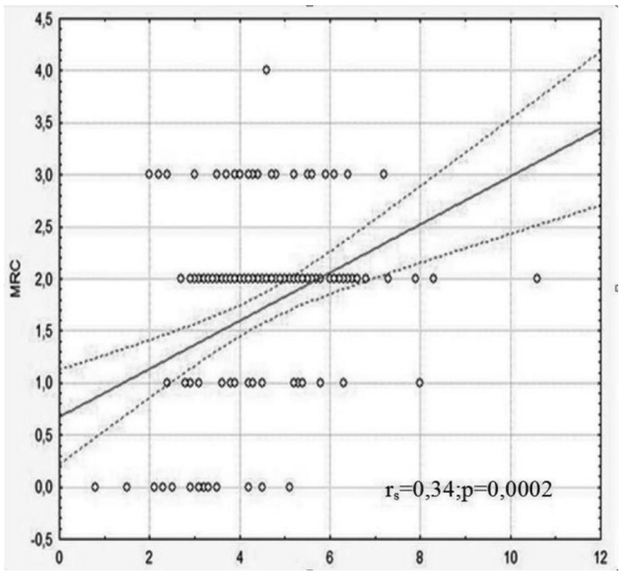

Fig. 10. Correlation between severity of breathlessness (MRC) and index echogenicity of external intercostal muscle

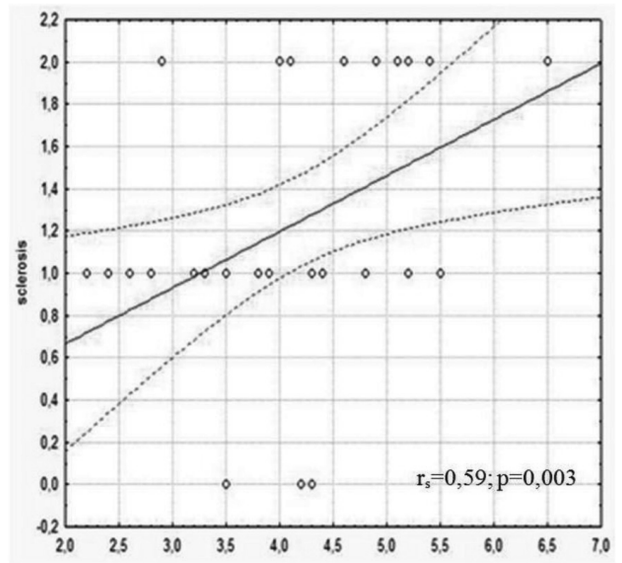

Fig. 11. Correlation between sclerosis manifestations and index echogenicity of abdominal internal oblique muscle

ultrasonic method of RM research proposed by us is simple and safe. In the light of the aforesaid, we compared the possibilities of these two diagnostic methods for estimation of RM status in COPD patients with different severity. Thus, sensitivity and specificity of this ultrasonic method was defined in 55% and 59% for estimation of sclerotic changes in RM as compared with the results of morphological research. Both prognostic positive and prognostic negative results of this ultrasonic method made 57%. Thus, the likelihood ratio for the positive result was 1,34. We did not detect a significant difference between ultrasonic and morphometric methods according to the estimation of sclerotic changes (χ^2=0,82; p=0,37) in COPD patients who underwent this trial.

Sensitivity and specificity of this ultrasonic method were defined both in 55% for estimation of expressiveness of fatty tissue intergrowth into the muscular tissue. Prognostic positive as well as prognostic negative results of this ultrasonic method made both 55%. Thus, the likelihood ratio for positive result =1,20. No significant difference according to this morphological phenomena (χ^2=0,36; p=0,55) between the ultrasonic and morphometric methods was revealed.

Sensitivity and specificity of ultrasonic method were defined in 55% and 59% to estimate atrophic muscular tissue expressiveness. Prognostic importance of positive result and negative result made both 57%. Thus, the likelihood ratio for positive result =1,33. We did not detect significant difference comparing COPD patients who underwent the examination by both the ultrasonic and morphometric methods (χ^2=0,82; p=0,37) according to the estimation of atrophic muscular tissue expressiveness. The accuracy of ultrasonic method was lower than that of morphological method in diagnosing RM dystrophic changes in accordance with the other analyzed morphological signs.

Conclusions

1. The proposed echodensitometric parameters showed heterogeneity of RM pathological changes and reflected in a complex way the dynamics of the degenerative processes occurring in RM during COPD progression. Thus, more dystrophic changes were detected in the following RM: sternocleidomastoid, external intercostal, abdominal internalexternal oblique and rectus. So, in $COPD_1$ the tendency to increased IH and ISD as well as decreased IE was observed, whereas in $COPD_2$ there was a tendency to decreased IH and ISD, while IE was increased. In $COPD_3$ the tendency to re-raising of IH and ISD against the background of IE decrease was detected. The greater difference was detected according to IE between COPD groups.
2. Increase of breathlessness in COPD patients positively correlated with IE and negatively correlated with ISD of sternocleidomastoid, internal intercostal, abdominal external oblique and rectus muscles.
3. High information value of this ultrasonic method for estimation of some dystrophic changes in RM was revealed. That gives grounds to consider this method as a choice for monitoring RM pathologic changes during COPD progression.

References

1. *Абросимов В.Н. Респираторная мышечная дисфункция и ее диагностика у больных с хронической обструктивной болезнью легких / В.Н. Абросимов, И.Б. Пономарева, Н.А. Осычная // Клиническая геронтология. - 2008. - №6. - С. 38-43.*
2. *Авдеев С.Н. Легочная гиперинфляция у больных ХОБЛ / С.Н. Авдеев // Пульмонология и аллергология. - 2006. - №2. - С. 11-16.*
3. *Авдеев С.Н. Хроническая обструктивная болезнь легких как системное заболевание / С.Н. Авдеев // Пульмонология. - 2007. - №2. - С. 104-116.*

4. *Безденежных А.В. Саркопения: распространенность, выявление и клиническое значение / А.В. Безденежных, А.Н. Сумин // Клиническая медицина. - 2012. - №10. - С. 16-23.*
5. *Оценка функции диафрагмы у больных хроническими заболеваниями легких по данным ультразвуковых методов исследования / Е.Г. Суркова, А.Л. Александров, В.Е. Перлей, А.Ю. Гичкин // Ученые записки СПбГМУ им. акад. И.П. Павлова. - 2009. - №2. - С. 28-32.*
6. *Перцева Т.А. Мышечная дисфункция при ХОБЛ: переоценка проблемы, новые возможности терапии / Т.А. Перцева // Здоров'я України. - 2008. - №3/1. - С. 17.*
7. *Платонова И.С. Морфологические изменения дыхательных мышц у больных хронической обструктивной болезнью легких с разной степенью дыхательной недостаточности: автореф. дис. на соиск. ученой степени канд. медиц. наук: 14.00.15 / И.С. Платонова. - Санкт-Петербург, 2003. - 18 с.*
8. *Чучалин А.Г. Нарушение функции дыхательных мышц при хронических обструктивных заболеваниях легких / А.Г. Чучалин, З.Р. Айсанов // Терапевтический архив. - 1988. - №8. - С. 126-132.*
9. *Age differences in knee extension power, contractile velocity, and fatigability / J.K. Petrella, J.S. Kim, S.C. Tuggle [et al.] // J. Appl. Physiol. - 2005. - Vol. 98. - P. 211-220.*
10. *Agusti A.G. Systemic effects of chronic obstructive pulmonary disease / A.G. Agusti, A. Noguera, J. Sauleda // Eur. Respir. J. - 2003. - Vol. 21. - P. 347-360.*
11. *Bernarg S. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease / S. Bernarg // Am. J. Respir. Crit. Care Med. - 1998. - Vol. 158. - P. 629-634.*
12. *Casaburi R. Impacting patient-centered outcomes in COPD: deconditioning / R. Casaburi // Eur. Respir. Rev. - 2006. - Vol. 15. - P. 42-46.*
13. *Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease / S. Levine, L. Kaiser, J. Leferovich, B. Tikunov // N. Engl. J. Med. - 1997. - Vol. 337. - P. 1799-1806.*
14. *Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle / J. Jobin, F. Maltais, J.F. Doyon [et al.] // J. Cardiopulm Rehabil. - 1998. - Vol. 18. - P. 432-437.*
15. *Contractile properties of the human diaphragm during chronic hyperinflation / T. Similowski, S. Yan, A.P. Gauthier [et al.] // N. Engl. J. Med. - 1991. - Vol. 325. - P. 917-923*
16. *Cullen M.J. Morphological changes in dystrophic muscle / M.J. Cullen, F.L. Mastaglia // British Medical Bulletin. - 1980. - Vol. 36. - P. 145-152.*
17. *Effects of testosterone and resistance training in men with chronic obstructive disease / R. Casaburi, S. Bhasin, L. Cosentino [et al.] // Am. J. Respir. Crit. Care Med. - 2004. - Vol. 170. - P. 870-878.*
18. *Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study / H. Watz, B. Waschki, C. Boehme [et al.] // Am. J. Respir. Crit. Care Med. - 2008. - Vol. 177. - P. 743-751.*
19. *Fitting J.W. Respiratory muscles in chronic obstructive pulmonary disease / J.W. Fitting // Swiss Medical Weekly. - 2001. - Vol. 131. - P. 483-486.*
20. *Franssen F.M. Sarcopenia in COPD functional and metabolic implications / F.M. Franssen // Eds.: A. Schols, E. Wouters. - Maastricht University, 2009. - 248 p.*
21. *Garcia-Rio F. Daily physical activity in patients with COPD is mainly associated with dynamic hyperinflation / F. Garcia-Rio // Am. J. Respir. Crit. Care Med. - 2009. - Vol. 180. - P. 506-512.*
22. *Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease NHLBI/WHO workshop report. - Access mode: http://www.goldcopd.org.*
23. *Impact of weight loss on physical function with changes in strength, muscle mass, and muscle fat infiltration in overweight to moderately obese older adults: A randomized clinical trial / A.J. Santanasto, N.W. Glynn, M.A. Newman [et al.] // J. Obesity. - 2011. - Vol. 2011. - ID 516576.*
24. *Laghi F. Disorders of the respiratory muscles / F. Laghi, M.J. Tobin // Am. J. Respir. Crit. Care Med. - 2003. - Vol. 168. - P. 10-48.*
25. *Mador M.J. Skeletal muscle dysfunction in chronic obstructive pulmonary disease / M.J. Mador, E. Bozkanat // Respiratory Research. - 2001. - Vol. 2. - P. 216-224.*
26. *Muscle-specific overexpression of IGF-I improves E-C coupling in skeletal muscle fibers from dystrophic mice / J.D. Schertzer, C. Van der Poel, T. Shavlakadze [et al.] // Am. J. Physiol. Cell. Physiol. - 2008. - Vol. 294. - P. 161-168.*
27. *Myosin heavy chain gene expression changes in the diaphragm of patient with chronic lung hyperinflation / J.J. Mercadier, K. Schwarz, S. Schiaffino [et al.] // Am. J. Physiol. - 1998. - Vol. 274. - P. 527-534.*
28. *O'Donnell D.E. Physiology and consequences of lung hyperinflation in COPD / D.E. O'Donnell, P. Laveneziana // Eur Respir Rev. - 2006. - Vol. 15. - P. 61-67.*
29. *Orozco-Levi M. Structure and function of the respiratory muscles in patients with COPD: impairment or adaptation? / M. Orozco-Levi // Eur. Respir. J. - 2003. - Vol. 22, Suppl. 46. - P. 41-51.*
30. *Physical activity in patients with COPD / H. Watz, B. Waschki, T. Meyer, H. Magnussen // Eur. Respir J. - 2009. - Vol. 33. - P. 262-272.*
31. *Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study / B. Waschki, A. Kirsten, O. Holz [et al.] // Chest. - 2011. - Vol. 140. - P. 331-342.*
32. *Sarcopenic obesity: definition, cause and consequences / S. Stenholm, T.B. Harris, T. Rantanen [et al.] // Curr. Opin. Clin. Nutr. Metab. Care. - 2008. - Vol. 11. - P. 693-700.*
33. *Sharp J.T. The respiratory muscles in COPD / J.T. Sharp // Am. Rev. Respir. Dis. - 1986. - Vol. 134. - P. 1089-1091.*
34. *Skeletal muscle and mortality results from the InCHIANTI Study / M. Cesari, M. Pahor, F. Lauretani [et al.] // J. Gerontol. - 2009. - Vol. 64A. - P. 377-384.*
35. *Subcellular adaptation of the human diaphragm in chronic obstructive pulmonary disease / M. Orozco-Levi, J. Gea, J.L. Lloreta [et al.] // Eur. Respir. J. - 1999. - Vol. 13. - P. 371-378.*
36. *Tkác J. Systemic consequences of COPD / J. Tkác, S.F. Man, D.D. Sin // Therap. advances in Respir. Dis. - 2007. - Vol. 1. - P. 47-59.*
37. *Ultrasound measurement of quadriceps wasting in patients with GOLD stage II COPD and its relationship to physical activity / D. Shrikrishna, R. Tanner, M. Patel [et al.] // Eur. Respir. J. - 2011. - Vol. 38, Suppl. 55. - P. 889.*
38. *Van Eeden S.F. COPD: A Chronic Systemic Inflammatory Disease / S.F. Van Eeden, D.D. Sin // Respiration. - 2008. - Vol. 75. - P. 224-238.*
39. *Wouters E.F. Nonpharmacological modulation of dynamic hyperinflation / E.F. Wouters // Eur. Respir. Rev. - 2006. - Vol. 15. - P. 90-95.*

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ИЗМЕНЕНИЯ СОСТОЯНИЯ ДЫХАТЕЛЬНОЙ МУСКУЛАТУРЫ ПРИ ПРОГРЕССИРОВАНИИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ

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Резюме

В статье освещены результаты одномоментного рандомизированного клинического исследования по оценке состояния вспомогательной дыхательной мускулатуры у пациентов с хронической обструктивной болезнью легких с учетом степени ее тяжести. Данные ультразвуковой денситометрии сопоставлены с результатами морфологического исследования внутренней косой мышцы живота.

Ключевые слова: хроническая обструктивная болезнь легких, саркопения, дыхательная мускулатура, ультразвуковая денситометрия.