Practical Medicine

Under bronchial obstruction caused by the bronchial asthma (BA), one may observe a change in blood gas factor, development of oxidative stress, electrolyte and metabolic imbalance, which lead to lung emphysema and chronic respiratory failure formation. This was accompanied by changes in respiratory muscles, particularly in the diaphragm, which are characterized by an advanced atrophy and a further loss of muscle strength and mass. The question arises to which extent BA affects the state of skeletal muscles as they determine tolerance for physical activity and quality of life in these patients. The purpose was to determine functional capacity of skeletal muscles and frequency of sarcopenia in patients with BA. Materials and methods. Seventy people aged 47.82 ± 13.54 years were examined. The first group included 35 persons who had BA, while the second group consisted of 35 healthy persons. An 8-step test for walking speed was applied to assess the functional capacity of skeletal muscles. The skeletal muscle power was evaluated with the help of spring hand dynamometer. Circumference of the tibia determined the criterion of satisfactory muscle mass. Quality of life was assessed by means of O.S. Chaban’s questionnaire. Results. When evaluating skeletal muscle power, wrist dynamometry was reduced by 22 % in case of severe BA compared to moderate BA, the corresponding index made 29 % when compared to the wrist dynamometry of healthy persons. An inverse correlation was found between BA severity and wrist strength in females (r = –0.65) and males (r = –0.3); walking speed in females (r = –0.72) and males (r = –0.6); circumference of the tibia in females (r = –0.17) and males (r = –0.28). A decrease in skeletal muscle power and tolerance for physical activity were associated with the loss of muscle component among 80 % of patients with BA. Conclusions. Sarcopenia was diagnosed in 5.71 % of persons from the control group, and in 25.71 % of patients with BA. Depending on BA severity and the age of patients, sarcopenia was detected in 9.5 % of patients who had moderate BA, and in 35.71 % of patients with severe BA; in 10.53 % of persons under the age of 45, and in 31.25 % of those over 45. Keywords: bronchial asthma; dysfunction of respiratory muscles; skeletal muscles; sarcopenia

Bronchial asthma as a pathophysiological factor of sarcopenia onset

Introduction

Bronchial asthma (BA) is a global problem: there are over 334 million sick people, of whom 250 thousands die annually due to complications caused by the disease. WHO specialists predict a 100-million increase in the number of asthma patients by 2025. Incorrect treatment of BA may significantly influence quality of life, lead to hospitalization, and result in a steadily decreased performance [1]. Chronic heterogeneous inflammatory disease of the respiratory tract accompanied by episodic whooshing rales, asphyxiation, feeling of tension in the chest and cough, manifests itself in the case of BA in different phenotypes and endotypes [2]. The phenotype of the disease and related pathology affect the dynamics of the disease, as well as reaction to traditional mode of treatment and development of complications in every individual patient [3].

In case of bronchial obstruction, the apparatus of external respiration, including respiratory muscles, performs a vast amount of work which leads to dysfunctions. Poor performance of respiratory muscles may be a result of exhaustion of energy supplies due to the growing need for energy [4]. It was proved that patients with BA, whose external respiratory function is reduced, maintain their physical activity by an excessive activation of anaerobic metabolic processes and increased energetic activity. Thus, maximum physical activity of patients with a moderate BA, irrespective of the stage of the illness, showed no effective functioning of the muscular system due to a limited supply of oxygen.

As a result, muscular energy consumption increases because of lactic acid excess and homeostasis shift [4, 5] towards acidosis.
Insufficient work of inspiratory muscles leads to a hypoventilation, while insufficient work of expiratory muscles leads to a development of dynamic hyperinflation, which makes removal of phlegm rather difficult [6]. The defects of respiratory mechanics, chronic inflammation, frequent worsening of the disease, electrolyte and metabolic imbalance accelerate formation of steady chronic hyperinflation of the lungs, which is one of the reasons of weak respiratory muscles [7]. Long-term bronchial obstruction leads to a development of chronic respiratory failure and overexertion of respiratory muscles decreasing their ability to generate maximum respiratory effort [8].

The process of respiratory muscles dysfunction development in case of BA is determined by complicated patho-physical mechanisms, in particular, by a chronic progressive worsening of external respiratory function (ERF), changes in blood gas composition, by oxidative stress, etc [9, 10]. Due to a chronic inflammation accompanied by an intoxication syndrome, low physical activity, and also to glucocorticosteroid (GCS) treatment, changes occur in the respiratory muscles, including changes in the diaphragm, which are characterized by progressive atrophy with a consequent loss of muscular strength and mass [8]. It is known that, in case of BA, a dysfunction of skeletal muscles also develops, which implies loss of muscle mass, weakness of skeletal muscles [11], development of sarcopenia.

According to the consensus of the European Working Group on Sarcopenia in Older People (EWGSOP, 2010), sarcopenia is a syndrome characterized by a progressive and generalized decrease in skeletal muscular mass and its capacity accompanied by a risk of development of such complications as reduced mobility, reduced quality of life and death [12].

Incidence of sarcopenia varies (5-70 %) with regard to age, sex, and ethnic origin. However, there are no present-day data related to a change in skeletal muscles condition in case of diseases accompanied by a reduction of the pulmonary functional reserve. At the same time, it shouldn’t be excluded that sarcopenia may be an independent process which promotes a systemic inflammation and progressing of the chief complaint. That is why assessment of the condition of both respiratory and skeletal muscles is so important, as it determines tolerance to the physical activity of the people diagnosed with BA.

In this context, the purpose of this work is to determine the functional capacity of skeletal muscles and frequency of sarcopenia development in patients with BA.

Materials and methods

The survey was conducted with participation of 70 patients, aged 28-72 (average age 47.82 ± 13.54), 38 of them being males (54.29 %) and 32 females (45.71 %). The patients participated in the survey only on condition of their voluntary consent regarding to the aim of the survey and the scope of the planned research. The patients under survey were divided into 2 groups made of 35 people, represented in accordance with their age and sex, 19 male patients and 16 female patients. The first group was composed of 35 patients with BA in remission: 21 patients (60.0 %) with a moderate BA, and 14 patients (40.0 %) with a severe BA. All the patients received a standard basic therapy of remission period which included inhalation GCS (i-GCS) and β2-agonist of long-acting and short-acting effect to manage BA symptoms. The other group of the survey participants (the control group) was composed of 35 healthy persons.

While making BA diagnosis, the following factors was taken into consideration: anamnesis, clinical symptoms, ERF indicators, obstruction reversibility by means of broncholytics. Selection of patients based on the degree of BA was carried out in accordance with criteria of the Edict № 128 of the Ministry of Health of Ukraine of 03.19.2007 «On approval of clinical protocols of medical care provision in Pulmonology and Edict № 688 of the Ministry of Health of Ukraine of October 8, 2013 «Unified clinical protocol of primary, secondary (specialized) medical care. Bronchial asthma» [13].

Peak expiratory flow rate indicator was applied for daily monitoring of the degree of obstruction. It was determined by means of «Vitalograph®» individual peak flow meter (manufactured by Boehringer Ingelheim № 43.400BOV).

Strength of skeletal muscles was estimated by means of DRP-10 flat-spring dynamometer, which is squeezed with the hand of the stretched upper limb. The squeezing force (kg) is indicated by an arrow on a special scale of the dynamometer. The size of tibia circumference was used to determine muscle mass. In order to estimate functional abilities of skeletal muscles, an 8-step test was performed for determining walking speed.

Sarcopenia was diagnosed according to the EWGSOP (2010) criteria in case of muscle mass (tibia circumference <31 cm), strength (<20 kg for women and <30 kg for men) and function (<0.8 m/s) loss. To diagnose sarcopenia, two of the three above mentioned criteria should be present, the first criterion being mandatory. The 1st stage – presarcopenia – is characterised by a loss of skeletal muscle mass without loss of strength and function; the 2nd stage – sarcopenia – is characterised by a loss of skeletal muscle mass accompanied by loss of strength and function; the 3rd stage – severe sarcopenia – is characterised by loss of all three criteria [12].

In order to determine patient’s adaptation to the disease as well as his/her ability to perform regular functions, a «quality of life» (QL) integral indicator is used. QL indicator was studied on the basis of the patient’s self-evaluation via Chaban Quality of Life Scale – CQLS, made of 10 questions related to physical and mental aspects of QL [14].

Statistical analysis determined parametrical indicators (average values (M) and their standard deviation (SD), Student’s criterion for independent sampling, Pearson correlation coefficient and non-parametric sampling). Differences in the indicators were considered accurate at p < 0.05. Statistica 6.0 program package was used for the analysis.
Results and discussion

Identification of functional capabilities of skeletal muscles led to the following results: reduction in walking speed was observed in 8 (50.0 %) women diagnosed with asthma, strong inverse correlative connection was established (r=-0.72) between the age and walking speed in case of a severe BA as compared to a moderate one and the control group. As for the women from the control group, slowing of walking speed was found only in 4 of them (25.0 %). Slowing of walking speed was found in 9 men (47.37 %), moderate inverse correlative connection (r = -0.6) was observed between age and walking speed. Slowing of walking speed was found only in 3 men (15.79 %) from the control group. Average indicators of walking speed with regard to age, sex and severity of BA are shown in table 1.

According to the results of dynamometry, reduction in power/strength of skeletal muscles was diagnosed in 17 patients with BA (48.57 %) (10 women and 7 men). Meanwhile, the female group demonstrated a significant inverse correlative connection (r=-0.65) between age and hand strength by 22.0 % in case of a severe BA, compared to the women with a moderately severe BA, and by 29.0 % compared to the control group. The men demonstrated a poor inverse correlative connection (r = -0.30) between their age and strength of hand. Reduction of carpal dynamometry by 15.0 % was observed in case of a severe BA, compared to those who suffered from a moderately severe BA, and by 17.0 % – compared to the control group. Only 4 women (25.0 %) of the control group demonstrated indicators of walking speed lower by 18.4 %, hand strength — lower by 29.2 %, and tibia circumference – lower by 21.4 % than the corresponding indicators of the control group (Table 1). When the total dose of i-GCS in the course of the disease was over 5 mln mkg, walking speed decreased by 25.2 %, hand strength – by 54.4 %, and tibia circumference – by 31.3 %, compared to the control group (Table 2).

Indicators of tibia circumference that meet diagnostic criteria of sarcopenia were found in 6 women (18.75 %) and 3 men (7.89 %) participating in the survey. Poor negative correlation between age and tibia circumference was observed (r=-0.17 and r=-0.28 correspondingly for men and women). Thus, tibia circumference of women under 45 with a severe BA was 28.0 ± 3.7 cm, while this parameter in women over 45 was – 25.0 ± 3.5 cm, which is significantly different (p<0.05) from similar indicators of the control group (30.0 ± 1.4 cm and 30.0 ± 2.5 cm correspondingly). As for the men under 45 with a severe BA (33.0 ± 2.1 cm), along with the men who had a moderately severe BA (37.0 ± 1.6 cm), a significant difference was observed (p<0.05) compared to the control group (43.1 ± 0.7 cm).

However, a significant difference (p<0.05) in male patients over 45 was determined only when patients with a severe BA were compared to the control group (27.2 ± 3.1 cm versus 36.4 ± 1.8 cm) (Fig.1 and 2).

Today, an adverse effect of systemic GCS on skeletal muscles has been well researched [15]. Direct correlation was found between a daily intake of GCS and weakness of skeletal muscles [16]. Unlike the systemic GCS, i-GCS have a less pronounced influence on the human body due to their localized effect on the respiratory system [17], that’s why i-GCS are generally considered safe when taken in low doses. Meanwhile, a cumulative effect in case of high doses of i-GCS and their long use leads to a risk of adverse events, such as thinning of the skin, loss of bone mass and muscle mass, decreased adrenal gland function, diabetes, pneumonia and cataract [18, 19].

Given the above mentioned data, the survey study of the state of skeletal muscles in patients with BA, depending on the total dose of i-GCS, is of scientific interest. Thus, patients whose total dose of i-GCS in the course of the disease made less than 5 mln mkg demonstrated indicators of walking speed lower by 18.4 %, hand strength — lower by 29.2 %, and tibia circumference — lower by 21.4 % than the corresponding indicators of the control group (Table 3). When the total dose of i-GCS in the course of the disease was over 5 mln mkg, walking speed decreased by 25.2 %, hand strength – by 54.4 %, tibia circumference — by 31.3 %, compared to the control group.

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Table 1. Functionality of skeletal muscles (m/s) according to age and severity of BA (M ± SD)

| Groups under survey, n= | Walking speed, m/s | Severe BA, n=14 | Moderate BA, n=21 | Control group, n=35 |
|-------------------------|---------------------|-----------------|------------------|-------------------|
| Women under 45          | 0.70 ± 0.10         | 0.85 ± 0.09     | 1.00 ± 0.20      |
| Women over 45           | 0.50 ± 0.11 *       | 0.60 ± 0.11     | 0.80 ± 0.11      |
| Men under 45            | 0.78 ± 0.07         | 0.90 ± 0.05     | 1.00 ± 0.33      |
| Men over 45             | 0.56 ± 0.13         | 0.70 ± 0.10     | 0.82 ± 0.15      |

Note. Mark * denotes reliable difference in indicators compared to the control group.

Table 2. Indicators of hand strength (kg) in accordance with age, sex and severity of BA (M ± SD)

| Groups under survey, n= | Walking speed, m/s | Severe BA, n=14 | Moderate BA, n=21 | Control group, n=35 |
|-------------------------|---------------------|-----------------|------------------|-------------------|
| Women under 45          | 16.0 ± 2.8          | 19.0 ± 1.7      | 21.0 ± 0.9       |
| Women over 45           | 11.0 ± 2.3 *        | 15.0 ± 2.2      | 17.0 ± 1.3       |
| Men under 45            | 27.0 ± 4.1          | 33.0 ± 3.8      | 37.0 ± 3.4       |
| Men over 45             | 19.0 ± 5.2 *        | 28.0 ± 4.1      | 34.0 ± 3.2       |

Note. Mark * denotes a significant difference in indicators compared to the control group.
The survey study established a strong inverse correlation ($r=-0.8$) between the total dose of i-GCS in the course of the disease and hand strength, moderate inverse correlation was established between the total dose of i-GCS in the course of the disease and walking speed ($r=-0.5$) and tibia circumference ($r=-0.3$) ($p<0.05$).

Considering the diagnostic criteria EWGSOP (2010), sarcopenia was diagnosed in 5.71 % of the participants of the control group and in 25.71 % of patients with BA. Pre-sarcopenia was found in 4 patients with BA, which corresponds to the incidence of 11.43 %. The indicators of dynamometry made $23.75 \pm 2.6 \, \text{kg}$, tibia circumference — $29.75 \pm 2.8 \, \text{cm}$, walking speed — $0.95 \pm 0.09 \, \text{m/s}$.

Sarcopenia was found in 3 persons (8.57 %). The indicators of dynamometry of those patients amounted to $19.25 \pm 5.3 \, \text{kg}$, tibia circumference — $28.25 \pm 1.58 \, \text{cm}$, walking speed — $0.76 \pm 0.05 \, \text{m/s}$ (difference between the indicators of dynamometry and tibia circumference compared to the control group is significant, $p<0.01$). Severe sarcopenia was diagnosed in 2 patients (5.71 %), whose indicators of dynamometry made $12.7 \pm 2.4 \, \text{kg}$, tibia circumference — $26.64 \pm 1.21 \, \text{cm}$, walking speed — $0.63 \pm 0.01 \, \text{m/s}$ (difference is significant as compared to the control group, $p<0.01$).

Establishment of dependency on the severity of BA, patient's age and basic therapy made it possible to diagnose sarcopenia in 9.5 % of patients with a moderately severe BA, and in 35.71 % — with a severe BA; in 10.53 % of persons aged under 45, and in 31.25 % — aged over 45; in 16.7 % of patients with a total dose of i-GCS under 5 mln mkg in the course of the disease, and in 21.74 % of patients — with over 5 mln mkg of i-GCS.

Consequently, the results of the survey demonstrate a correlation between development of skeletal muscle dysfunction and sarcopenia depending on the severity of BA, cumulative effect of i-GCS and the patients' age.

The obtained results are consistent with the data presented by certain authors who found that at the initial stage of bronchial obstruction respiratory muscles respond to an increase in their functional load with a hypertrophy. However, in the process of the disease progression, the force of muscular contractions decreases, and they are acquiring atrophic changes [20, 21]. Research of the respiratory muscles performed by other authors found that patients with the lowest degree of obstructive irregularities had the highest degree of functional irregularities in the work of respiratory muscles. The authors attribute the decrease in muscular respiratory strength to a long-lasting cough and incoordination...
of muscular activity due to a compensatory increase in muscular strength as a response to a long performance under bronchial obstruction [22].

Assessment of the state of respiratory and skeletal muscles is important as it makes it possible to determine tolerance to physical activity of the patients with bronchial obstruction. The latter depends not only on the degree of intensity of pulmonary pathology [23], but also on extra-pulmonary manifestation of the disease [24]. This is confirmed by the results of research related to alveolar ventilation during physical activity, and the authors consider static hyperinflation of the lungs to be the reason for its worsening. They found a correlation between the volume of breath and the degree of ventilation of the dead space in respiratory cycle (r=-0.74, p=0.0048) [25].

Degenerative-dystrophic changes in skeletal muscles, including respiratory muscles, lead to a decrease in tolerance to physical activity, development of respiratory failure, deterioration in the quality of life of patients with chronic obstructive lung disease [26]. Considering the data, we’ve carried out a research related to the quality of life of patients diagnosed with BA, and compared their results with the ones of the control group. It was found that 51.4 % of the patients report a low and very low quality of life versus corresponding to 25.7 % in the control group (Fig. 3).

In accordance with the results of subjective assessment of their state, caused by severity of the disease, it was found that patients with a moderate BA had a higher life quality (61.9 % of cases), while patients with severe BA had a lower one (42.9 %). It is likely that a severe bronchial obstruction and long anamnesis of the disease make the patients get used to the load of the pathology, and for this reason they consider their state of health in a more optimistic way [27]. 47.6 % of patients with a moderate BA had certain restrictions regarding their daily activities due to their health, in case of a severe BA, this indicator increased to 57.1 %.

Comparison of the survey’s results with the data of specialized literature makes it possible to assume that the key role in pathophysiological mechanisms of sarcopenia development in patients with BA belongs to the inflammatory process which is accompanied by changes in blood gas composition, oxidative stress, increase in level of anti-inflammatory cytokines circulating in blood flow (IL-1, 2, 6; interferon-γ, TNF-α), which in their turn result in a lower synthesis of muscular protein, proteolysis of heavy chain myosin, lower testosterone level and increase in catecholamine synthesis [28].

**Conclusions**

1. 25.7 % of patients with BA and 5.7 % of the control group respondents were diagnosed with sarcopenia. Depending on the severity of BA and the age of patients, sarcopenia was found in 9.5 % of patients with a moderately severe BA, and in 35.71 % of patients with a severe BA; in 10.53 % of individuals under 45, and in 31.25 % of individuals over 45 years of age.

2. Correlation was established between the severity of BA on the one hand, and reduction of hand strength — on the other hand. Inverse correlation was established between the age of patients with BA and their walking speed: inverse correlation in women (r=-0.65) and men (r=-0.3).

3. Correlation was established between the age of patients with BA and their walking speed: inverse correlation in women (r=-0.72), and inverse moderate correlation in men (r=-0.6).

4. Development of sarcopenia depends on the pattern of basic therapy. In BA patients, sarcopenia was found in 16.7 % of those whose total dose of i-GCS for the period of the disease was under 5 mln mkg, and in 21.74 % of those whose total dose of i-GCS for the period of the disease was over 5 mln mkg.

5. 51.4 % of respondents among those diagnosed with BA claim they have a poor or very poor quality of life, which exceeds almost twice the corresponding indicator of the respondents in the control group.

**Information about the contribution made by each author:** N.P. Masyk — concept and design of the survey. Analysis of the data obtained, the article composing; S.I. Ponina — collection and processing of the materials. Analysis of the data obtained, presentation of the text.

**Conflicts of interests.** Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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*Fig. 3. Indicators of the quality of life of patients with bronchial asthma as compared to the control group*
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Бронхіальна астма як патофізіологічний чинник формування саркопенії

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Резюме. Актуальність. В умовах бронхіальної обструкції при бронхіальній астмі (БА) розвиваються зміни газового складу крові, оксидативний стрес, електролітний і метаболічний дисбаланс, що сприяють формуванню еміграції лейкогенів і інших дихальних недостатності. При цьому виникають зміни дихальних м'язів, зокрема у діафрагми, що характеризуються прогресуючою атрофією з наступною втратою м'язової сили й маси. Мета: визначення функціональних можливостей скелетних м'язів і частоти розвитку саркопенії у хворих на БА. Матеріали та методи. Обстежено 70 осіб віком 47,82 ± 13,54 року. Першу групу становили 35 пацієнтів, які хворіють на БА, другу — 35 здорових осіб. Для оцінки функціональних можливостей скелетних м'язів застосували 8-кілометровий тест визначення швидкості ходьби. Силу скелетної мускулатури оцінили за допомогою опитувальника О.С. Чабана. Результати. При оцінці сили скелетної мускулатури встановлено зменшення показників кистьової динамометрії на 22 % при тяжкому перебігу БА порівняно з показниками здорових осіб. Встановлено кореляційні зв'язки між тяжкістю БА і силою кисті в жінок (r = –0,65) і чоловіків (r = –0,3); швидкістю ходьби в жінок (r = –0,72) та чоловіків (r = –0,6); окружністю гомілки у жінок (r = –0,17) і чоловіків (r = –0,28). Зниження сили м'язів і толерантності до фізичного навантаження ассоціювалося з втратою м'язової здатності в 80 % пацієнтів з БА. Висновки. Саркопенія діагностована у 5,71 % осіб контрольної групи і у 25,71 % хворих на БА. Залежно від тяжкості БА і віку хворих саркопенія виявлена у 9,5 % пацієнтів із середньотяжкою БА і у 35,71 % — із тяжкою БА; у 10,53 % осіб віком молодших 45 років і у 31,25 % — старших 45 років.

Ключові слова: бронхіальна астма; дисфункція дихальних м'язів; скелетна мускулатура; саркопенія

Бронхіальна астма як патофізіологічний фактор формування саркопенії

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