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Cardiopulmonary testing of patients with bronchial asthma

Key words: *bronchial asthma, cardiopulmonary testing, cardiorespiratory system, physical activity.*

Among numerous internal diseases, a special place is occupied with bronchopulmonary diseases, in particular, bronchial asthma (BA). Based on findings of the domestic and foreign researches, BA prevalence rate annually grows, regardless of improved diagnostic, preventive and treatment methods [27, 28]. For the last decades, the BA incidence has considerably increased among the young population. Moreover, the number of severe and drug-resistant forms of the disease rises.

Currently, we lack data on functional coordination of inter-system connections among central, pulmonary system, cardiohemodynamics, hemorheology and homeostasis in physical activity of patients with BA, as these comprise the macrolevel and microlevel of blood circulatory systems that play main and organizing roles in a human body. The degree of its compensatory abilities affects vital and working ability prognosis for the patients [23, 30–32]. A heart, which timely-changed intensity of work is required for most adaptation reactions of a body, often turns into a place where adaptation transits into injury [4, 9, 12, 17, 25]. However, the blood circulatory system itself is immediately affected with ventilation embarrassments which are the key BA-causing factors[13–15, 18, 21, 42]. The status of autonomic nervous system (ANS) is of major importance too [3, 11, 19, 20]. There can hardly be found a pathological form, development and course of which would remain unaffected with this system: in some cases, it is the main cause of pathogenesis;in other cases, it gives a consequential response to injury of any body systems and tissues [78, 79].

If BA is viewed from position of functional systems theory (FST), it is worth stressing that a human body is a complex multi-functional system, which regulation is subordinated to certain rules and mechanisms, interaction of which affects functioning of the whole body. Body activity is stipulated with the functional system dominating in terms of survival and adaptation to environment [1]. Clinical presentation of BA rests upon broncho-obstructive syndrome, being multi-form in terms of formation mechanism, thus stipulating heterogeneity of BA pathogenesis with similar clinical presentation. Respiratory system is a dominating one, and it should be contemplated, due to anatomic and functional interrelation with a cardiovascular system (CVS), within a unified cardiorespiratory system. Performance of effectory systems is conditioned with the peculiarities of their regulation. Central nervous system (CNS) and autonomic nervous system (ANS) are known to have regulatory functions, as well as humoral-mediator and immune systems. Their dysregulation is one of pathogenic mechanisms leading to vegetative neurosis, and it disorders vegetative support of effectory systems functioning connected with homeostasis maintenance [33, 38].

Study of vegetative regulation in patients with BA is currently related not only to deeper insight into pathogenesis processes, but also with the necessity of new data from the standpoint of developing new approaches to therapy. With a view of topicality pertaining to remedial treatment and physical rehabilitation of patients with BA, the issues of determining the patients capacity to maximum exercise, i.e. physical working capacity, are of particular interest. Physical working capacity is a human potential ability for maximal effort during dynamic, static or mixed-type activity. Such studies were acknowledged by WHO as reasonable, especially this refers to estimation of body functional reserves and differential diagnostics of cardiac disorders, development of load-adequate and safe motion regime for the patients, as well as the physical rehabilitation programs. However, the reality limited the researchers' aspirationsrelated to identification of responses to exercise which is,firstly, similar, in terms of its properties, to the exercise made in day-to-day life, and is, secondly, quite significant. The latter allows to identify an important indicator of the body functional state, in particular, tolerance to various exercise, in other words, the body capacity to tolerate it without change of its state [30, 37, 44].

There are many kinds of clinical exercise tests developed for objective estimation of the body functional reserves. Some tests are simple and do not require any special equipment, however, they give general information; others give full estimation of all system functions involved in the exercise, but they require complex equipment.

Numerous walk tests were developed: timed walk tests (2-, 5-, 6-, 9- and 12-minute), fixed distance walk tests,variously-rated walk tests (rate is chosen by the patient, rate is set by the researcher, walk rate is constant throughout the test or gradually increases) [8, 11, 41]. The most common among them is a 6-minute walk test.It is simple and does not require any special equipment. This test gives a general idea of human functional capacity, but it does not provide with any specific information about functions of individual organs and systems involved in the exercise, including the load-limiting mechanism. This test assesses sub-maximal physical capacity: the majority of patients do not reach maximal load for 6 minutes, as they choose the intensity rate themselves. Almost all kinds of daily exercise are done at sub-maximal level, therefore 6-minute test is better in reflecting the patient's functional capacity required in day-to-day life [35]. It is worth noting that 6-minute walk test does not allow to determine maximal oxygen consumption (MOC) during exercise, to identify the reason of panting or to define the mechanisms of decreased tolerance to exercise. However, many researches revealed a close connection between the 6-minute walk test result and maximal oxygen consumptionmeasured with ergometric bicycle or treadmill during the research. There is no consensus, whether treadmill should be used for 6-minute walk test. Many authors consider that walking along a corridor and treadmill walking give various load to the patients, therefore, they waste various energies; other authors find them quite comparable. Nevertheless, each of these methods feature its own advantages. Treadmill requires less space and allows for regular monitoring of the patient condition during the exercise (gaseous exchange, ECG etc.);however, a patient is more used to walking along a corridor, and it does not require any complex equipment and reflects day-to-day exercise to a greater extent. However, results of 6-minute walk test are largely conditioned with influence of subjective factors, with the patient's motivation being the principal one. Another subjective factor affecting the test results is a correctness degree of the research performed by an instructor. Moreover, the effect of training is also significant: results of re-testing usually exceed the previous results;moreover, the incremental value may reach 17 % [36, 47].

Increasingly more attention is paid to shuttle-test with growing walking pace. Conditions of its performance allow for considerable reduction of subjective factors influence. For this purpose, treadmill speed is changed every other minute in accordance with the protocol design. Shuttle-test is effective both in a corridor and with a treadmill in a closed room. However, it is worth noting that its results do not also allow for assessment of bronchial obstruction severity. For full understanding of functional state the cardiorespiratory system during the exercise, an advanced research should be performed in order to study its capacity to maintain gaseous exchange in lungs and tissues under stressful physical work [48, 51, 52, 54, 57].

Preferences are currently given to bicycle ergometry and treadmill, as they allow for precise amount of exercise and ensure working of large ground of muscles. In foreign references, such researches are united under a general notion of CPET (cardiopulmonary exercise testing). Testing with treadmill features some advantage over bicycle ergometry: most patients are used to walking rather than cycling [100]. Moreover, such exercise involves more muscles, thus leading to larger stress, and, consequently, higher maximal oxygen consumption (exercise on treadmill is by 5–10 % higher than with ergometric bicycle) [5, 6, 16, 53]. The major disadvantage of treadmill is that it is difficult to determine precisely the amount of work done. For exercise on treadmill, the patient's weight is highly important. It is worth stressing that metabolic value of exercise may be affected with the patient's resting upon the treadmill handrails. The key advantage of bicycle ergometry is that it allows for easy determination of the work done, moreover, such exercise is more appropriate for the patients suffering from obesity. Ergometric bicycle occupies less space. Bicycle ergometry makes blood pressure check and ECG monitoring possible. Notwithstanding that both devices are used clinically, ergometric bicycle is preferred [22, 34].

Cardiopulmonary exercise testing is often used in clinical practice to diagnose diseases with panting during exercise and reduced tolerance to exercise. Test results allow for objective assessment of body functional reserves, gaining of valuable information about each system involved in the test, and identification of mechanisms that limit making the exercise. Along with ventilation indicators measured at rest, exercise tests may be used for the patients suffering from lung diseases in order to prevent risks of after-surgery pulmonary complications [40, 50]. Exercise test, according to numerous scientists, is a basic component required to assess lung restoration in patients with chronic obstructive pulmonary disease (COPD), BA and other chronic pulmonary diseases.

Domestic and foreign researchers developed a range of exercise test protocols. In European countries, studies of physical working capacity in patients with chronic non-specificpulmonary diseases (CNPD) widely apply P. Nowacki's test with gradually increasing load of 2 minute long and growing power by 0.25 W / kg of the tested person weight. With such approach to exercise dosing, patients with various body weight benefit from equal test conditions, which enable comparison of data obtained from patients of various weight groups. In order to assess maximal capacity, this approach offers an exercise with growing power that rises momentarily or every other minute from 5–25 W until refusal, i.e. until first signs of intolerance to exercise [35].

Bronchodilator effectiveness control is increasingly often assessed according to a fixed exercise protocol, which implies an exercise complying with usual routine load – 50 W on ergometric bicycle or 3 miles per hour on a treadmill for at least 6 minutes. This test may be carried out in one hour or more after intensive testing [43].

High-intensity fixed exercise protocols are widely applied (70–80 % of due exercise level) in order to show effects of broncholytic therapy, rehabilitation programs, and by some authors – as a means to choose and assess the treatment performed [7, 15, 24].

Recent recommendations of the European Respiratory Society and American Thoracic Society offered a test protocol with gradually-increasing bicycle ergometry load. This test consists of a resting phase, 3-minute phase of free pedaling, a load period and a restoration period. During the second period, load is increased every 3 minutes from 5 to 25 W, depending on the patient severity. The exercise lasts 10–12 minutes or until reaching maximal characteristics: subjective and objective criteria of intolerance to exercise. According to P. Palange, test with increasing bicycle ergometry load is considered a gold standard for assessment of physical working capacity in patients with obstructive pulmonary diseases. This protocol is widely applied in practice [58]. Strivings for reduced cost related with exercise tests and decreased influence of physical fatigue underpinned development of a method with 1- or 2-minute increase of load. Exercise tests were carried out among healthy persons with each stage lasting 1 or 2 minutes. It was concluded that the majority of results obtained during gradual growth of exercise load every other minute or every 2 minutes are comparable, especially at maximal or peak load.

It is reasonable to remind of an intermittent exercise protocolwhich consists of short periods: 3–4-minute load intermitted with periods of rest, withthe exercise load progressively increasing. However, this protocol is rarely used clinically [59].

In order to identify hyperactivity of respiratory tract, bronchoprovocation with exercise is used. Bronchial spasm caused by exercise is regarded by numerous authors as one of manifestations pertaining to non-specific bronchial hyperactivity. Among the factors that condition bronchoconstriction development during exercise, a leading place is occupied with increased respiratory heat and moisture consumption. Thistestislesssensitivethanbronchoprovocation with metacholine, acetylcholine or histamine. K. Holzer confirmed that many patients have negative results of an exercise test and positive result of chemical assay;in the meantime they also reported a back reaction [60].

ATS recommends to use two kinds of exercise protocols. The first one: gradually-increasing exercise test (initial load – 60 % of due value at the first minute, 75 % – at the second minute, 90 % – at the third, and 100 % – at the fourth minute). As soon as the expected heart rate or ventilation rate is achieved, the exercise should be continued for at least 4 minutes more. The second test: a fixed exercise protocol lasting 6–8 minutes, where exercise comprises 45–60 % of due value of maximum breathing capacity. This test is recommended to be used in patients with more marked disorder of external respiration function. Spirometry should be taken before and after the load at minute 5, 10, 15, 20, 30 of rest. Forced expiratory volume (FEV_1) is a key indicator used to assess the results. Some authors make earlier measurements – at minute 1 and 3 after exercise, while bronchial spasm may sometimes occur as soon as the exercise is finished. ERS School Courses recommend to measure FEV_1at minute 1, 3, 5, 7 and 15. This test is considered positive if FEV_1 is more than 10 % [61, 62].

So, what happens during a cardiorespiratory exercise test? A body responses to any stress with a regulatory systems effort and mobilization of adaptation mechanisms, with some people showing moderate effort response and other people exhibiting full-blown effort of regulatory systems to similar-intensity influence. It depends on body reserves and state of health. Application of functional exercise tests is physiologically substantiated with one of the most important systemic regularities formulated by P. K. Anokhin: «A body responses to any influence with a change of several physiological functions and selection of optimal regime of life activity under new conditions. The nature of transient responses at this moment reflects the peculiarities of relevant regulatory mechanisms and may be served as their quality criterion».

Factors that define physical working capacity include: a respiratory function, ventilation-perfusion balance, a cardiac function, regulation of peripheral circulation, muscles metabolism. A respiratory function consists of a great number of components, with the main ones: bronchial patency, diffusion capacity, lung elasticity and respiratory muscle function. Each of the abovementioned components has a functional capacity margin which affects the extent to which the patient's physical activity will be limited. Study of a functional capacity margin is only possible under stressful exercise. Muscular physiology itself is based on coordinated function of respiratory, cardiovascular and muscular systems. Failure of any these systems may lead to impaired tolerance to exercise. Tolerance to exercise may be defined as the body capacity to ensure maximal supply of oxygen during intensive exercise [7, 13–15, 47, 49]. Oxygen supply system consists of the following functional components:

- a respiratory function which includes pulmonary mechanics and respiratory muscles work, as well as the mechanisms of ventilation regulation;
- ventilation-perfusion balance, oxygen diffusion;
- change of heart rate and systolic volume;
- distribution of blood flow favoring the working muscles;
- muscular metabolism which includes functions of oxidizing and glycolytic enzymes.

Irrespective of considerable reserves of a body, even an insignificant aberration of any element joining the oxygen supply system manifests with decrease of maximal oxygen consumption (MOC), being the major indicator of cardiorespiratory system efficiency, which also serves as an extent of aerobic capacity and an integral indicator of oxygen transporting system. While exercise is a kind of stress, exercise tests enable detection of first signs of pulmonary and cardiovascular pathology, which, at the state of rest, are 'concealed' by the body reserve capacities [34]. In healthy persons, MOC is restricted with the capacity of oxygen transporting function of heart and the muscles ability to extract and utilize oxygen supplied with blood flow to ensure aerobic metabolism. In persons with cardiorespiratory pathology – MOC is restricted with the extent of respiratory and cardiac failure, and disorder of tissue metabolism [24, 25, 31]. Maximal oxygen consumption is largely affected with general physical fitness. Trained sportsmen have MOC nearly twofold exceeding the normal rate inherent to people with a usual lifestyle. For example, MOC in exercising athletes may increase more than 20 times and reach up to 80 ml/ min/kg. Moreover, aging people that take sports lifelong have a large functional reserve of cardiovascular system if compared to «inactive» people of the same age [12, 36, 37, 38]. Build-up of cardiovascular functional reserve during exercise test is initially achieved at the expense of increased systolic volume and higher heart rate.During sub-maximal and maximal exercise, further growth of cardiac output occurs only due to rising heart rate. Rising heart rate is, firstly, stipulated with decreased influence of parasympathetic nervous system, and secondly, with increased sympathetic activity. Maximal heart rate reduces with aging. Cardiac output in healthy people of one age group varies in terms of systolic volume rate. As a rule, it is higher formen, fortaller and fit persons. Forhealthy people, heart rate during exercise increaseslinearly with a rise of maximal oxygen consumption (MOC). Achievement of due heart rate reflects maximal or sub-maximal effort and is regarded as achievement of maximal oxygen consumption (MOC). This maximal value is not recommended to be achieved in patients, and it is a stringent condition to stop. In patients with pulmonary diseases, maximal heart rate usually fails to achieve due values, and pulse may be higher than it should be for such level of maximal oxygen consumption, and with the disease progress, the heart rate reserve grows, and oxygen pulse (OP) falls. OP decrease reflects hemodynamic effects of dynamic hyperinflation [46, 47]. Maximal oxygen consumption, like the external work, usually rises during exercise almost linearly until maximaloxygen consumption is reached. Further increase of capacity is undurably maintained with anaerobic metabolism with development of lactic acidosis. MOC to WR ratio is a so-called rate of oxygenvalue of work (MOC/WR), and does not depend on sex, age, or height, and reflects effectiveness of metabolic conversion of chemical energy into mechanical work [48, 49].

Hemodynamic parameters during exercise test change as follows. Systolic blood pressure may grow as high as 220 mm Hg at peak load, and diastolic blood pressure, at the same time, remains within normal range, i.e. below 90 mm Hg. Blood pressure decline during exercise is an abnormal phenomenon, therefore, the test must be stopped immediately. Moreover, it should be taken into account that increased cardiac output and the associated pulmonary blood flow during exercise cause moderate growth of pressure in a pulmonary artery. Forpatients with pulmonary pathology, additional involvement of pulmonary vessels into blood circulation and their dilation lead to considerable reduction of pulmonary vascular resistance. And if a healthy person has its blood pressure rising in a pulmonary artery until cardiac output enhances 2–3 times, patients with bronchial asthma, however, may start to exhibit insignificant pulmonary hypertension even at the state of rest. Normally, blood pressure in a pulmonary artery rises during exercise, and in case of bronchial asthma, especially its grave form, resistance in pulmonary vessels during exercise remains constant or slightly grows. Factors stipulating pulmonary hypertension in case of BA include: vasospasm, re-modeling of pulmonary arteries, and destruction of capillary bed in the result of emphysema (at later stage of the disease). In order to overcome the mentioned blood flow obstructions and to ensure normal perfusion, pressure should be increased. Development of pulmonary hypertension and pulmonary heart are a consistent result of long-lasting course of obstructive pulmonary diseases (BA, obstructive bronchitis) [50]. In opinion of many scientists, normal pressure in a pulmonary artery and normal general pulmonary resistance at the state of rest do not always witness absence of any pulmonary hemodynamics disorders, as they do not exclude concealed pulmonary hypertension attributable to changed pulmonary circulation, which are revealed during exercise or at the phase of acute inflammation in bronchi. The more bronchial obstruction grows, the more systolic, diastolic and mean pressure in a pulmonary artery increases [51].

Another important indicator of cardiovascular functional state is the speed of heart rate restoration. During exercise, healthy people response to increased metabolic needs with arespiratory minute volume (RMV) both at the expense of respiration rate (RR) and enhanced breathing capacity (BC). Breathing capacity grows approximately up to 50 % of vital capacity, and ventilation is further increased mostly at the expense ofrespiration rate, as increased respiration is a more saving way to enhance ventilation at heavy exercise. To determine, whether any limitation of physical working capacity (PWC) is a result of ventilation disorders, it is necessary to measure maximal pulmonary ventilation (MPV). In healthy people, RMV at MOC usually ranges from 60 to 70 % of maximal pulmonary ventilation. The remaining 30 40 % of MPV, which are not used, are the respiratory reserve. Availability of this reserve means that in healthy people maximal physical working capacity is limited with cardiovascular factors rather than ventilation factors [52]. Maximal pulmonary ventilation is better to regard as a criterion for a forced capacity of a respiratory apparatus, its maximal «output» conditioned with properties of the respiratory muscles, pulmonary and airways biomechanics. With the disease progress, respiratory minute volume is often limited with obstructive disorders of external respiration function, which leads to dynamic hyperinflation manifesting with increased respiration rate and reduced breathing capacity [53, 54]. Consequently, respiratory muscles endure greater load. Another nature of ventilation response to maximal exercise is described in relevant references.In the authors' opinion, patients with broncho-obstructive pulmonary diseases have much higher ventilation than it is expected, due to increased ventilation of dead space, insufficient gaseous exchange and enhanced ventilation demand which lead to lowering of physical working capacity and peripheral muscle dysfunction [55–57]. Increase of respiratory rate in patients during exercise results in reduced expiratory timeand, consequently, to decreased air evacuation from alveoli, in other words, «trapped air» grows. In its turn, increased pulmonary hyperinflation impedes deeper breathing, thus creating a vicious cycle. Such limitation of breathing capacity under conditions of enhanced respiratory efforts during exercise reflects neuro-mechanical dissociation of respiratory apparatus, which, in its turn, contributes greatly to panting intensity in patients with bronchial asthma during exercise [58–61].

Physical activity is also affected with functional state of a nervous system. Global researches showed that patients with bronchial asthma, especially the ones with a long-lasting course of the disease, exhibit various clinical signs of nervous system injury, both central and autonomic. Such patients reveal changes of brain potentials, which prove dysfunction of stem, mesodiencephalic and limbic-reticular complexes. And these changes, in their turn, worsen the asthma course [62].

Moreover, the role of infection factor in the course of asthma was proved with numerous studies. Some authors associate disorders of myocardial activity in patients with asthma with long-lasting persistence of pathogenic and opportunistic microbial population and with effects of two factors: infectious-toxic and allergic (mediator) [26, 46].

Currently, scientific material is being actively collected, which refers to disorders of cardiorespiratory functional state in patients with bronchial asthma and reasons that cause such disorders.

Conclusion

Exercise testing of patients with bronchial asthma, its analysis and forecasts are of immediate interest, as it will allow for development of new methods to diagnose, treat and prevent appearance and progression of cardiorespiratory disorders, and allow for improved quality of life in this category of patients.

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КАРДИОПУЛЬМОНАЛЬНОЕ ТЕСТИРОВАНИЕ БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ

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Резюме

На сегодняшний день недостаточно данных о функциональной координации межсистемных связей центральной, легочной, кардиогемодинамики, гемореологии и гемостаза в физической активности больных БА, ведь они составляют макро - и микроуровневые системы кровообращения, играют в организме человека основную и организующую роль. Учитывая актуальность восстановительного лечения и физической реабилитации больных БА, особый интерес представляют вопросы определения способности пациентов к предельным физическим усилиям, то есть – физической работоспособности. Существует много разновидностей клинических нагрузочных тестов для объективной оценки функциональных резервов организма. С использованием одних можно получить основную информацию – эти методы просты в исполнении и не требуют специального оснащения, другие дают полную оценку функции всех систем, задействованных в выполнении пробы, и требуют сложного оборудования. В настоящее время предпочтение отдается велоэргометрии и тредмилу, поскольку они позволяют точно дозировать нагрузку и обеспечивают участие в работе крупных групп мышц.

Кардиопульмональное тестирование с нагрузкой все чаще используется в клинической практике для диагностики заболеваний, сопровождаемых одышкой при физической нагрузке и снижением толерантности к физической нагрузке. Результаты пробы позволяют объективно оценить функциональные резервы организма, получить важную информацию о каждой из систем, участвующих в выполнении пробы, и помочь в определении механизмов, лимитирующих выполнения физической нагрузки. Нагрузочное тестирование является основным компонентом для оценки легочного восстановления у больных ХОБЛ, БА и другими хроническими болезнями легких.

Проведение тестирования с физической нагрузкой у больных бронхиальной астмой, его анализ и прогнозирование актуально, что позволит разработать новые способы диагностики, лечения и профилактики возникновения и прогрессирования нарушений кардиореспираторной системы и улучшить качество жизни у данной категории больных.

Ключевые слова: *бронхиальная астма, кардиопульмональное тестирование, кардиореспираторная система, физическая активность.*

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CARDIOPULMONARY TESTING OF PATIENTS WITH BRONCHIAL ASTHMA

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Summary

Currently, we lack data on functional coordination of inter-system connections among central, pulmonary system, cardiohemodynamics, hemorheology and homeostasis in physical activity of patients with BA, as these comprise the macrolevel and microlevel of blood circulatory system that play main and organizing roles in a human body. With a view of topicality pertaining to remedial treatment and physical rehabilitation of patients with BA, the issues of determining the patients capacity to maximum exercise, i.e. physical working capacity, are of particular interest. There are many kinds of clinical exercise tests developed for objective estimation of the body functional reserves. Some tests are simple and do not require any special equipment, however, they give general information; others give full estimation of all system functions involved in the exercise, but they require complex equipment. Preferences are currently given to bicycle ergometry and treadmill, as they allow for precise amount of exercise and ensure working of large ground of muscles.

Cardiopulmonary exercise testing is increasingly often used in clinical practice to diagnose diseases with panting during exercise and reduced tolerance to exercise. Test results allow for objective assessment of body functional reserves, gaining of valuable information about each system involved in the test, and identification of mechanisms that limit making the exercise. Exercise test is a basic component required to assess lung restoration in patients with chronic obstructive pulmonary disease (COPD), BA and other chronic pulmonary diseases.

Exercise testing of patients with bronchial asthma, its analysis and forecasts are of immediate interest, as it will allow for development of new methods to diagnose, treat and prevent appearance and progression of cardiorespiratory disorders, and allow for improved quality of life in this category of patients.

Key words: *bronchial asthma, cardiopulmonary testing, cardio-respiratory system, physical activity.*

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