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Efficacy of ginkgolides and bilobalides for prevention of decreased physical activity in patients with bronchial asthma

Key words: *bronchial asthma, physical activity, cardiorespiratory system, ginkgolides and bilobalides.*

So far, the problem of physical working capacity in patients with bronchial asthma (BA) has become extremely topical, since most patients are young and physically active people. The issue of determining patients' ability to achieve critical physical effort, specifically, anaerobic threshold (AT), is of particular interest. The term «physical working capacity» is used to denote potential human ability to express maximum efforts under conditions of dynamic, static or mixed work. Anaerobic threshold is a point in physical activity when insufficient delivery of oxygen to working muscles triggers anaerobic energy supply mechanisms with generation of lactic acid, which leads to increased production of carbon dioxide (CO_2) and non-linear ventilation increase.

The WHO finds physical working capacity studies rational and helpful, especially when it comes to evaluation of organism's functional reserves and differential diagnosis of cardiac activity disorders, design of sufficient and safe motion mode for the patients and development of physical rehabilitation programs.

The factors affecting the «physical working capacity» are:

- respiratory function, including pulmonary mechanics and respiratory muscles work, as well as mechanisms of ventilation regulation;
- ventilation-perfusion ratios, diffusion of oxygen;
- heart function, including changes in heart rate and stroke volume;
- control of peripheral circulation, i.e. the ability to distribute blood flow in favour of working muscles;
- muscle metabolism, including functions of oxidative and glycolytic enzymes.

Muscle physiology itself is based on coordinated functioning of the respiratory, cardiovascular and muscular systems. Lack of one of these systems may lead to poor tolerance of physical activity. The study of functional safety margin is only possible in conditions of stress, because physical activity is a kind of stress that helps detecting the initial signs of pathology of pulmonary and cardiovascular systems, which are «masked» by reserve capacity of the organism while resting. It is an established fact that in patients with bronchial asthma with reduced respiratory function (RF) physical working capacity is supported due to anaerobic metabolism. Changes in performance of the respiratory system affect efficiency of muscle activity by limiting oxygen supply to them. Anaerobic threshold is the indicator of this process. Its decline in patients with bronchial asthma is associated with the rising energy cost of breathing and decrease in respiratory ventilation.

At maximum physical activity in patients with moderate persistent bronchial asthma, regardless of the phase of the disease, there is no effective performance of both pulmonary and cardiovascular systems. In response to physical activity the respiratory minute volume is increasing only through respiration rate, systolic blood pressure and heart rate are increasing excessively, consequently, the heart is unable to provide adequate minute volume of blood for covering energy consumption in the muscles, removal of excess lactic acid and maintaining homeostasis of the body.

It has been established that in 100 % of patients with moderate persistent bronchial asthma in case of acute exacerbation of the disease the metabolic equivalent of task (MET) decreases on average to (4.8 ± 1.6) kcal/kg, the work performance level drops to (68.6 ± 4.7) %, and anaerobic threshold lowers to (48.9 ± 3.2) %. Also there is an average reduction of the oxygen cost of work performance

of (71.2 ± 2.1) %, deterioration of average oxygen (O_2) consumption effectiveness indices: V'O_2 to (78.5 ± 2.5) %. Merely (75.6 ± 6.2) % of patients reach the anaerobic threshold.

During remission of the disease in 46.7 % of patients with bronchial asthma the oxygen cost of work is significantly normalized to an average of (14.8 ± 1.5) ml/min/W, but in 53.3 % of patients no significant changes are observed, oxygen consumption in the metabolic equivalent of task (MET) units remains reduced in the group by 10.3 %, exercise tolerance (W) to (78.6 ± 4.3) % and (1.2 ± 0.1) W/kg, oxygen consumption peak (VO_2) to (88.4 ± 4.1) %. Merely (86.7 ± 6.2) % of patients in the group reach the anaerobic threshold.

Therefore, it is extremely important to develop and implement new prevention methods against the decline in physical activities with a view to improve the quality of life of patients with bronchial asthma.

The work is based on the method of prevention of reduction of physical working capacity in patients with bronchial asthma as a prototype, which involves simultaneous administration of basic treatment medications – inhaled corticosteroids and short-acting β2-agonist – and prescription of bronchodilators (long-acting theophyllines) – Theopec, 600 mg daily for 1 month (see M.G.Gireeva. Anaerobic threshold and physical working capacity in patients with bronchial asthma [Text]: Author's abstract of Doctoral Dissertation. 14.00.43: presented on 16.01.1991: approved on 16.07.1991 / Mariam Gireevna Gireeva. – Dagestan, 1991. – 23 p. – Bibliography. 23 p. – 200522022).

Yet, the drawback of this method is that prolonged and frequent use of long-acting theophyllines, especially in maximum daily dose, leads to unwanted side effects, namely: cardiotoxic effect (arrhythmia, angina spuria, increased frequency of angina attacks, tachycardia, fluctuations in blood pressure), as well as general weakness, decreased performance and drowsiness.

The utility model is based on the task of development of a prevention method against the decline in physical working capacity in patients with bronchial asthma, which uses a medicinal product based on ginkgolides and bilobalides against the background of standard treatment chosen for the period of remission to achieve an increase in metabolic and oxygen cost of work and level of its performance, improvement of oxygen consumption efficiency and muscle activity during physical activities, normalization of functioning of the cardiovascular system for improvement of the quality of life of such patients.

The task is solved by additional prescription of a 90-day course of a medicinal product containing ginkgolides and bilobalides in the compendial dose and regimen against the background of administration of an inhaled glucocorticosteroid and a short-acting β2-agonist, according to the utility model during remission, which is a method of prevention of the decline in physical working capacity in patients with bronchial asthma.

The method is based on investigation of new data on identification of hidden pathological changes in cardiorespiratory system at maximum physical activity in patients with BA, and their role in the disease during treatment with inhaled corticosteroid drugs. Bilobil Intens, a complex medicinal product based on flavonoid glycosides and terpene compounds (ginkgolides and bilobalides), was used for the claimed method as a medicinal product containing ginkgolides and bilobalides. The active ingredients of the extract determine its specific pharmacological activity. The product is manufactured in the form of pink gelatine capsules filled with light to dark brown powder with visible dark particles (registration No.UA/1234/01/03 of 06.05.2010, valid till 06.05.2015). The product improves cerebral blood flow and oxygen and glucose supply to the brain tissue, prevents platelet aggregation inhibiting platelet activating factor, dilates blood vessels, improves blood circulation and protects cells and tissues from injuries caused by oxygen deficiency by regulation of metabolism. The product prevents development of toxic and traumatic brain oedema, age-related changes in the activity of cholinergic receptors and α2-adrenoreceptors. Flavonoids exhibit significant antioxidant effects. Bilobalides and ginkgolides have neuroprotective effects. The medicinal product improves blood rheology, sensory and cognitive functions of the brain and prevents deterioration of mental activity. The product is used for treatment of violation of cerebral blood flow and brain function (dementia syndrome in cases of primary degenerative dementia, vascular dementia or their combinations), which is manifested in deterioration of memory and mental activity, melancholia and anxiety, dizziness, tinnitus, headache and sleep disorders, blood circulation disorders in the lower extremities in presence of chronic obliterating angiopathy. The medicinal product can be taken without regard to food. The capsules should be swallowed with water.

The maximum therapeutic effect can be observed in 1 month. In order to achieve a sustainable effect Bilobil Intens shall be administered for at least 3 months, particularly in elderly patients. After 3 months of treatment, justification of further treatment shall be proven. The main contraindication for use is the individual drug intolerance. The adverse effect of the medicinal product may arise in the intestinal tract (rarely – disorders of the gastrointestinal tract), the nervous system (very rarely – headache), the immune system (very rarely – skin allergies (itching, redness and swelling).

There is no data on the use of medicinal products containing ginkgolides and bilobalides for prevention of physical working capacity deterioration in patients with bronchial asthma in the available literature.

The method is carried out as follows.

BA patients are prescribed a medicinal product containing ginkgolides and bilobalides – 1 capsule 2 times a day after meals for 90 days, immediately after the end of treatment of exacerbation. All patients receive standard medical therapy chosen for remission period, which includes the use of an inhaled corticosteroids and a short-acting β2-agonist for reversal of asthma symptoms.

The cardiorespiratory stress test was used in order to determine the degree of exercise intolerance and basic mechanisms of such disorders in patients with bronchial asthma (see Recommendations on the use of exercise testing

in clinical practice [Text] / P.Palange [et al.] // Eur. Respir. J. – 2007. – Vol. 29. – P. 185–209). Ergospirometry makes it possible to quantify physical working capacity and functional status of the respiratory and cardiovascular systems (including tissue respiration) and their interaction. Ergometer ER/2 and Ergoselect 1000 LP Basic with automatic power dissipation regardless of pedalling speed were used for graduated exercise. The main parameters of pulmonary ventilation and gas exchange, as well as the heart rate and electrocardiogram were recorded automatically and processed by Ergopnevmotest OM/05-Ts and the Oxycon Pro ergospirometric system – Version JLAB 4.67, manufactured by VIASYS Healthcare, which consists of a pneumotachograph with an integrator, oxygen analyzers and an ECG recorder. The cycloergospirometric study was conducted subject to the general testing requirements specified for submaximal physical activity. Prior to the study, those medications affecting the functional state of cardiorespiratory and nervous systems were cancelled. Smoking was prohibited for two or more hours prior to the study. Physical activity started no earlier than in 1 hour after meal. Absolute and relative contraindications for testing and conditions requiring special attention and care were taken into consideration based on the recommendations (see ERS School Courses ATS/ACCP Statement on Cardiopulmonary Exercise Testing [Text] // Am. J. Respir. Crit. Care Med. – 2006. – Vol. 167. – P. 211 – 277). Temperature conditions – from +18°C to +25°C, light clothing, breathable and moisture absorbent, light shoes with hard soles on feet. Prior to the beginning of the study the patients were informed about the purpose and procedures of the motor test. Load capacity, maximum oxygen consumption, minute lung ventilation and heart rate were predicted based on extrapolation method with a view to gender and anthropometric parameters of the patient under study. Physical working capacity was defined in compliance with the Protocol RA – 150 – I B3 – BP2 – EC1. The work continued to refuse or was stopped after appearance of subjective and objective symptoms that limited further increase of the load: severe shortness of breath, achievement of submaximal heart rate, appearance of electrocardiographic signs of coronary insufficiency. Deviation of pedalling rate from the given level (below 60 rpm) due to muscle weakness or lack of motivation for reaching the load limit was regarded as subjects' withdrawal from further tests. The maximum level of executed load was estimated as the limit of functional capacities of the body. The following parameters were evaluated:

• $V'O_2$, mL/min – oxygen consumption in mL per minute, measured at maximum load and at the level of anaerobic threshold;

• VO_2/kg, mL/min/kg – oxygen consumption in mL per minute per kilogram of body weight, measured at the maximum load and at the level of anaerobic threshold;

• BR, % – reserve ventilation at the maximum load;

• HR, L/min – patient's heart rate at the peak load;

• HRR, L/min – patient's heart rate reserve after reaching the maximum load;

• O_2/HR, mL – oxygen pulse, mL, observed at the maximum load;

• SpO_2, % – oxygen saturation measured at the maximum load;

• BP, mm Hg – patient's blood pressure at the peak load;

• W – maximum achieved load in Watts;

• MET – metabolic equivalent of task measured at the maximum load.

Each patient made an assessment of the reasons for termination of the test. Estimated indices were obtained through automatic calculation based on the developer's method.

Here are specific examples of application of the method.

Example 1 (based on the prototype method).

Patient S., female, 49, case history No.1170, has been treated at the Department of Obstructive Lung Diseases at the F.H.Yanovskiy National Phthisiology and Pulmonology Institute of the NAMS of Ukraine, SI, with the following diagnosis: moderate persistent III degree bronchial asthma,, exacerbation phase, VD II. The patient has been ill for more than 10 years. For the last 3 years the patient has been associating occurrence of exacerbations with hypothermia or the ARVI. The last exacerbation occurred 8 months ago. For the last 2 years the patient has been taking Flixotide 1,000 mg, 2 breaths daily, and Salbutamol as a short-acting bronchodilator. The patient was prescribed prolonged theophylline, Theopec, 1 capsule 2 times daily for 1 month in the course of the background treatment during remission. The patient underwent clinical and instrumental examination prior to the beginning of the treatment, immediately upon termination of the course of treatment with Theopec and in 3 months after the treatment based on the prototype method.

The patient's physical activity was decreased during exacerbations of BA, according to the cycloergospirometric study data, in particular: the MET rate decreased to 4.5 kcal/kg, duration of the 3rd phase of cardiorespiratory stress test decreased to 6.3 minutes, oxygen cost of work dropped to 14.9 mL/min/kg, peak oxygen consumption (VO_2) reduced to 75.9 %, oxygen consumption performance indices (O_2) decreased to: $V'O_2$ to 82 %, $V'O_{2p}$ to 84 %, and the maximum oxygen consumption at the peak load ($V'O_{2max}$) to 95 %. The patient's RER index descriptive of the ratio of production of CO_2 (VCO_2) to oxygen consumption (VO_2) was higher during exacerbation of BA and amounted to 1.15 units, which confirmed hyperventilation during the test. The patient's BR index assessing respiratory volumes was slightly reduced to 72 %, which is typical for bronchial asthma. The patient's dO_2/dW index descriptive of efficiency of muscle performance at the maximum physical activity was reduced to 8.6 ml/min/W. The indices descriptive of the cardiovascular system performance at maximum physical activity were slightly invigorated, in particular: HR/VO_2 (in absolute terms and in percentage terms) were slightly higher – 6.9 beats/mL/kg, dHR/dO_2 – 75.6 beats/min/mL, VO_2/HR – 76 % (see Table 1).

Forced expiratory volume per 1 second was 63.8 %, forced vital lung capacity was 72.5 %, peak expiratory flow rate was 70.5 %, the ratio of forced expiratory volume per 1 second to forced vital lung capacity was 70.6 %.

Table 1.
Cycloergospirometric test indices over time, patient S.

Indices	Patient S.		
	Exacerbation phase	immediately after treatment based on the prototype method	in 3 months after treatment based on the prototype method
1	2	3	4
Duration of the 3rd phase of the test (min)	6.3	6.5	6.4
$V'O_2$/kg (mL/min/kg)	5.9	5.3	5.3
$V'O_2$/kg (mL/min/kg), %	75.9	76.1	76.2
$V'O_2$ (%)	82	85	86
$V'O_{2p}$, (%)	86	86	86
$V'O_{2max}$ (%)	85	90	91
RER (relative units)	1.15	1.01	1.01
BR (%)	72	73	75
BP (% of $V'O_{2max}$)	38	37	35
W (%)	84	85	85
W (W/kg)	1.8	1.9	1.8
W (W)	156.3	159.8	157.6
dO_2/dW (mL/min/W)	8.6	8.1	8.2
HR/VO_2 (beats/mL/kg)	6.9	6.7	6.5
dHR/dO_2 (beats/min/mL)	75.6	72	71
VO_2/HR (%)	76	78	78
SpO_2 (%)	85	82	87
MET (kcal/kg)	5.8	5.5	5.2
RW (W/kg)	0.8	0.9	0.8
PMA (%)	74	75	78
Assessment of dyspnoea based on Borg scale before the test (points)	0	0	0
Assessment of dyspnoea based on Borg scale after the test (points)	2	2	2

The patient underwent repeated examination immediately after the course of treatment with Theopec in the course of the background therapy. The following was established: there were no significant changes in spirogram speed performance, in particular: forced expiratory volume per 1 second was 68.3 %, forced vital lung capacity was 73.2 %, peak expiratory flow rate was 72.4 %, the ratio of forced expiratory volume per 1 second to forced vital lung capacity was 71.6 %. There were no significant changes in cardiorespiratory stress test indices, in particular: exercise tolerance remained reduced to 5.5 kcal/kg, RW and PMA indices remained reduced as well – 0.9 W/kg and 75 %, respectively. The indices descriptive of the level of work performed remained unchanged (W) – 85 %, 1.9 W/kg, 159.8 W. The 3rd phase of the cardiorespiratory stress test lasted for 6.5 minutes. The indices descriptive of the oxygen cost of work remained reduced: $V'O_2$/kg to 5.3 mL/min/kg, $V'O_2$/kg, % -76.1 %, $V'O_2$ – 85 %, $V'O_{2p}$ – 86 %, $V'O_{2max}$ – 90 %. The patient's dO_2/dW index descriptive of the efficiency of muscle activity at the maximum physical activity was reduced to 8.1 mL/min/W.

The patient's indices descriptive of the cardiovascular system performance at maximum physical activity after the course of treatment with Theopec did not differ from those of the period of exacerbation: dHR/dO_2 – 72 beats/ml/min, VO_2/HR – 6.7 beats/ml/kg, VO_2/HR – 78 %. SpO_2 at maximum physical activity was 82 %, SBP (systolic blood pressure) – 156 mm Hg, DBP (diastolic blood pressure) – 77 mm Hg.

In 3 months after discontinuation of Theopec the patient underwent repeated examination. There were no significant changes in spirogram speed performance, in particular: forced expiratory volume per 1 second was 71.3 %, forced vital lung capacity was 83.2 %, peak expiratory flow rate was 74.8 %, the ratio of forced expiratory volume per 1 second to forced vital lung capacity was 72.3 %. The indices descriptive of oxygen cost of the work performed remained unchanged, in particular: $V'O_2$/kg – 5.3 mL/kg and 76.2 %, $V'O_2$ – 86 %, $V'O_{2p}$ – 86 %, $V'O_{2max}$ – 91 %. The RER index – 1.01, MET – 5.2 kcal/kg, RW (relative workload) – 0.8 W/kg, PMA – 78 %. Duration of the 3rd phase of the test – 6.4 minutes. There were no significant changes in the indices descriptive of the work performed as well: W – 85 %, 1.8 W/kg and 157.6 W, dO_2/dW – 8.2 mL/min/W.

The indices descriptive of effectiveness of cardiovascular response to exercise did not differ from the indices of the exacerbation period: dHR/dO_2 – 71 beats/mL/min, VO_2/HR – 6.5 bps/mL/kg and 87 %, SBP – 158 mm Hg, DBP – 78 mm Hg, SpO_2 – 87 %.

Thus, the course of treatment resulted in achievement of:

• a slight improvement in physical activity due to reserve capacity of the cardiovascular and respiratory system for up to 2 months with a further deterioration.

Yet, the administered treatment led to adverse events – an increase in body weight by 3 kg per month of administration of the medicinal product, a slight increase in blood glucose level, dyspepsia and mild abdominal pain shortly after administration of the medicinal product (disappeared

independently in 2 days of administration), an increase of complaints about premature ventricular contraction (PVC), especially in the evening.

Example 2 (based on the claimed method).

Patient P., female, 64, case history No.2054, admitted to the Department of Obstructive Lung Diseases at the F.H. Yanovskiy National Phthisiology and Pulmonology Institute of the NAMS of Ukraine, SI, with the following diagnosis: moderate persistent III degree bronchial asthma, exacerbation phase, VD II.

The patient has been ill for 14 years. The last exacerbation occurred 4 months ago. Over the last year the patient has been taking Seretide 50/500 μg, 2 breaths twice a day. Immediately after the inpatient treatment of the exacerbation of the disease the patient was prescribed a medicinal product containing ginkgolides and bilobalides (Bilobil Intens) according to the recommended treatment regimen: 1 capsule twice a day for 3 months in the course of the background treatment during remission, which included administration of an inhaled corticosteroids and a short-acting β2-agonist for reversal of asthma symptoms. Medical examination was conducted prior to prescription of the medicinal product, immediately upon termination of the course of treatment and in 3 months after the treatment.

Prior to prescription of the medicinal product the patient's forced expiratory volume per 1 second was 58 %, forced vital lung capacity was 71 %, peak expiratory flow rate was 68 %, and the ratio of forced expiratory volume per 1 second to forced vital lung capacity was 70 %.

The patient's physical activity was decreased during exacerbations of BA, according to the cycloergospirometric study data, in particular: MET rate decreased to 5.4 kcal/kg, duration of the 3rd phase of cardiorespiratory stress test was lowered to 6.2 minutes.

The indices descriptive of the oxygen cost were reduced, in particular: $V'O_2$/kg to 5.8 mL/min/kg and 75.5 %, $V'O_2$ to 83 %, $V'O_{2p}$ to 85 %, $V'O_{2max}$ to 84 %. The patient's dO_2/dW index descriptive of efficiency of muscle performance at the maximum physical activity was reduced to 8.8 ml/min/W, AT to 35 %. The indices descriptive of effectiveness of adaptation of the cardiovascular system at physical activity also showed ineffectiveness of its function, in particular: dHR/dO_2 to 49.5 %, HR/VO_2 to 3.3 beats/mL/kg, VO_2/HR to 82 % (see. Table 2).

The indicators descriptive of effectiveness of the work performed were reduced at exacerbation of the BA, in particular: W to 83 %, 1.9 W/kg and 154.2 W, dO_2/dW to 8.8 mL/min/W, MET 5.4 kcal/kg, RW to 0.8 W/kg, PMA to 77 %.

Improvement of cycloergospirometric indices was detected during examination immediately after administration of the medicinal product containing ginkgolides and bilobalides in the course of the background therapy during the period of remission. Specifically, the indices descriptive of the oxygen cost of work at the maximum physical activity were improved: $V'O_2$/kg was 6.3 mL/min/kg and 79,2 %, $V'O_2$ to 89 %, $V'O_{2p}$ 90 % $V'O_{2max}$ – 96 %, BP – 47 %.

The level of physical working capacity and exercise tolerance was increased, which was confirmed by improvement

Table 2.
Cycloergospirometric test indices over time, patient P.

Indices	Patient P.,		
	Exacerbation phase	immediately after treatment based on the claimed method	in 3 months after treatment based on the claimed method
1	2	3	4
Duration of the 3rd phase of the test (min)	6.2	6.9	7.4
$V'O_2$/kg, (mL/min/kg)	5.8	6.3	6.3
$V'O_2$/kg, (mL/min/kg), %	75.5	79.2	79.8
$V'O_2$, (%)	83	89	91
$V'O_{2max}$, (%)	84	96	98
$V'O_{2p}$, (%)	85	90	92
RER	1.16	0.98	0.96
BP (% of $V'O_{2max}$)	35	47	45
W, (%)	83	86	88
W, (W/kg)	1.9	2.1	2.0
W, (W)	154.2	174.5	172.6
dO_2/dW (mL/min/W)	8.8	9.1	9.2
dHR/dO_2, %	49.5	59.6	61.2
HR/VO_2 (beats/mL/kg)	3.3	3.6	3.5
dHR/dO_2 (beats/min/mL)	75.2	82.3	83.9
VO_2/HR, (%)	82	85	86
SpO_2, (%)	92	93	95
MET (kcal/kg)	5.4	6.5	6.2
RW, (W/kg)	0.8	0.9	1.1
PMA (%)	77	78	79
Assessment of dyspnoea based on Borg scale before the test (points)	0	0	0
Assessment of dyspnoea based on Borg scale after the test (points)	2	1	1

of their indices: W up to 86 % and 174.5 W, 2.1 W/kg, dO_2/dW – 9.1 mL/min/W, MET – 6.5 kcal/kg, RW – 0.9 W/kg, PMA – 78 %.

Also, there was improvement in the cardiovascular system performance indices: dHR/dO_2 – 82.3 %, HR/VO_2 – 3.6 beats/mL/kg, VO_2/HR – 85 %. Forced expiratory volume per 1 second was 65 %, forced vital lung capacity was 76 %, peak expiratory flow rate was 72 %, the ratio of forced expiratory volume per 1 second to forced vital lung capacity was 74 %.

Stabilization of physical working capacity indices was detected during examination in 3 months after the course of medicinal product containing ginkgolides and bilobalides, namely Bilobil Intens, in the course of the background therapy during the period of remission.

There was no drop in indices descriptive of the oxygen cost of work performed at maximum physical activity: $V'O_2/kg$ – 6.3 mL/min/kg and 79.8 %, $V'O_2$ – 91 %, $V'O_{2p}$ – 92 %, $V'O_{2max}$ – 98 %, BP – 47 %. Effectiveness of the work performed and exercise tolerance remained stable, no deterioration was observed: W – 88 % and 172.6 W and 2.0 W/kg, dO_2/dW – 9.2 mL/min/W, MET – 6.2 kcal/kg, RW – 1.1 W/kg, PMA – 79 %.

Cardiovascular system performance remained unchanged as well: dHR/dO_2 – 61.2 %, HR/VO_2 – 3.5 bps/mL/kg, VO_2/HR – 86 %. Forced expiratory volume per 1 second was 69 %, forced vital lung capacity was 78 %, peak expiratory flow rate – 82 %, the ratio of forced expiratory volume per 1 second to forced vital lung capacity was 80 %.

Thus, the course of the medicinal product containing ginkgolides and bilobalides in the course of the background therapy during the period of remission facilitated:

- improvement of efficiency of oxygen utilization by the body by increasing efficiency of its absorption at the time of maximum physical activity, which was confirmed by improvement of indices: $V'O_2/kg$ from 5.8 mL/min/kg and 75.5 % to 6.3 mL/min/kg and 79,8 %, $V'O_2$ from 83 % to 91 %, $V'O_{2p}$ from 85 % to 92 %;
- increase of exercise tolerance and level of work performed, which is confirmed by improvement of indices: W from 83 % and 1.9 W/kg and 154.2 W, dO_2/dW from 8.8 mL/min/W, MET from 5.4 kcal/kg, RW from 0.8 W/kg, PMA from 77 % to W – 88 % and 2.0 W/kg and 172.6 W, dO_2/dW to 9.2 mL/min/W, MET to 6.2 kcal/kg, RW to 1.1 W/kg, PMA to 79 %;
- improvement of the cardiovascular system performance, which is confirmed by improvement of indices: dHR/dO_2 from 75.2 % to 83.9 %, VO_2/HR from 82 % to 86 %.
- no adverse events were observed.

For the purpose of comparative assessment of the two methods aimed at prevention of reduction of physical working capacity in patients with bronchial asthma, all patients were divided into groups: the prototype method was used in 15 patients (Group I), the claimed method was used in 15 patients (Group II). There were 15 individuals in the group of healthy donors (control group). Age and gender composition of patients and the degree of severity of bronchial asthma were comparable in all groups.

During sample comparison of the percentage of healthy individuals and the same number of bronchial asthma patients it has been established that administration of Theopec as a part of combination treatment in patients with bronchial asthma based on the prototype method resulted in a positive trend in the estimated indices.

No statistically significant difference compared to the beginning of the treatment was observed.

Detailed analysis revealed that patients with bronchial asthma in Group I experienced a decrease in physical activity after exacerbation of the disease. Maximum work performance is achieved due to inefficient functioning of the cardiovascular and pulmonary systems at the maximum physical activity. Specifically, BA patients have lower oxygen supply during physical activity than healthy individuals as a result of inhibition of functional activity of the respiratory system. This is confirmed by reduced cycloergospirometric indices descriptive of the respiratory system function: $V'O_2/kg$ to (5.8 ± 1.2) mL/min/kg, $V'O_2/kg$ to (73.9 ± 2.4) %, $V'O_2$ to (82.9 ± 3.5) %, $V'O_{2p}$ (79.3 ± 3.3) %, $V'O_{2max}$ to (88.3 ± 2.4) %, RER to (1.02 ± 0.1). The indices descriptive of the cardiovascular system performance were reduced as well: dHR/dO_2 to (75.6 ± 6.5) %, HR/VO_2 to (7.1 ± 3.2) bps/mL/kg, HR to (124.1 ± 7.1) beats/min and (83.1 ± 5.8) %, VO_2/HR to (6.4 ± 3.2) beats/mL/kg and (71.3 ± 9.7) %, SBP to (184.2 ± 8.1) mm Hg, DBP to (70.5 ± 4.5) mm Hg, SpO_2 to (82.2 ± 8.5) %. As a result, exercise tolerance and level of work performed were reduced: W to (69.5 ± 3.6) % and (0.8 ± 0.2) W/kg, (96.4 ± 5.8) W, dO_2/dW to (7.2 ± 1.6) mL/min/W.

After the preventive course of long-acting theophyllines, in particular Theopec, with the background treatment in BA patients from Group I no significant changes were observed in the estimated indices compared with the beginning of the treatment: significant difference persisted compared to the group of healthy individuals in the following indices – $V'O_2/kg$ from (5.8 ± 1.2) mL/min/kg to (4.2 ± 1.4) mL/min/kg, $V'O_2/kg$ from (73.9 ± 2.4) % to (74.1 ± 2.2) %, $V'O_2$ from (82.9 ± 3.5) % to (86.5 ± 3.6) %, $V'O_{2p}$ from (79.3 ± 3.3) % to (77.9 ± 3.2) %, $V'O_{2max}$ from (88.3 ± 2.4) % to (89.8 ± 2.2) %. There were no significant changes in the cardiovascular system performance: VO_2/HR from (71.3 ± 9.7) % to (68.3 ± 9.2) %, HR/VO_2 from (7.1 ± 3.2) beats/mL/kg to (6.9 ± 3.1) beats/mL/kg, SpO_2 from (82.2 ± 8.5) % to (83.4 ± 8.5) %. As a result, exercise tolerance, level of work performed and physical activity of patients treated with Theopec were reduced. In particular: W changed from (69.5 ± 3.6) % to (71.5 ± 4.1) %, MET from (4.1 ± 1.3) kcal/kg to (4.7 ± 1.4) kcal/kg.

In 3 months after the treatment, the patients' physical activity remained lowered. The cardiovascular system performance during physical activity was ineffective: $V'O_2/kg$ from (5.8 ± 1.2) mL/min/kg to (3.3 ± 1,6) mL/min/kg, $V'O_2/kg$ from (73.9 ± 2.4) % to (75.3 ± 2.4) %, $V'O_2$ from (82.9 ± 3.5) % to (85.1 ± 4.1) %, $V'O_{2p}$ from (79.3 ± 3.3) % to (78.2 ± 3.6) %, $V'O_{2max}$ from (88.3 ± 2.2) % to (88.2 ± 2.4) %, the duration of the 3rd phase of the test from (6.3 ± 2.2) minutes to (6.3 ± 2.1) minutes, BP from

Table 3.

Cardiorespiratory stress test indices in patients with moderate persistent BA in Group I, (M ± m)

Indices	Healthy individuals	Patient Group I		
		Before treatment	Immediately after treatment based on the prototype method	In 3 months after treatment based on the prototype method
	(n = 15)	(n = 15)		
Duration of the 3rd phase of the test (min)	12,92 ± 3,2	6,3 ± 2,1#	6,4 ± 2,2#	6,3 ± 2,2#
$V'O_2$/kg (mL/min/kg)	7,7 ± 1,1	5,8 ± 1,2#	4,2 ± 1,4#	3,3 ± 1,6#
$V'O_2$/kg (%)	82,3 ± 5,6	73,9 ± 2,4#	74,1 ± 2,2#	75,3 ± 2,4#
$V'O_2$ (%)	102,3 ± 5,6	82,9 ± 3,5#	86,5 ± 3,6#	85,1 ± 4,1#
$V'O_{2p}$ (%)	94,3 ± 8,9	79,3 ± 3,3#	77,9 ± 3,2#	78,2 ± 3,6#
$V'O_{2max}$ (%)	99,3 ± 10,3	88,3 ± 2,4#	89,8 ± 2,2#	88,2 ± 2,4#
RER	0,95 ± 0,1	1,02 ± 0,1	1,06 ± 0,1	1,01 ± 0,1
AT (% of $V'O_{2max}$)	65,3 ± 4,3	48,1 ± 3,5	49,3 ± 3,6	48,9 ± 3,2
W (%)	92,9 ± 3,5	69,5 ± 3,6#	71,5 ± 4,1#	70,2 ± 4,1#
W (W/kg)	2,9 ± 1,1	0,8 ± 0,2#	0,9 ± 0,1#	0,89 ± 0,1#
W (W)	185,0 ± 6,3	96,4 ± 5,8#	95,9 ± 7,1#	94,5 ± 8,1#
dO_2/dW (ml/min/W)	11,42 ± 1,3	7,2 ± 1,6#	7,1 ± 1,6#	8,2 ± 1,8#
dHR/dO_2 (beats/min/ml)	78,6 ± 4,5	75,6 ± 6,5	78,5 ± 6,5	76,5 ± 5,9
$HR/V'O_2$ (beats/ml/kg)	2,7 ± 1,6	7,1 ± 3,2#	6,9 ± 3,1#	6,2 ± 2,8#
HR (beats/min)	112,5 ± 8,6	124,1 ± 7,1#	121,8 ± 7,1#	120,3 ± 6,9#
HR (%)	93,5 ± 9,2	83,1 ± 5,8#	86,9 ± 3,9	87,2 ± 4,2
$V'O_2$/HR (beats/ml/kg)	10,2 ± 2,6	6,4 ± 3,2#	6,8 ± 2,8	6,9 ± 2,2
$V'O_2$/HR (%)	88,6 ± 9,6	71,3 ± 9,7#	68,3 ± 9,2#	72,3 ± 8,2#
SpO_2 (%)	98,6 ± 8,2	82,2 ± 8,5	83,4 ± 8,5	82,9 ± 8,2
MET (kcal/kg)	8,4 ± 1,6	4,1 ± 1,3#	4,7 ± 1,4#	4,2 ± 1,2#
RW (W/kg)	1,2 ± 0,1	0,9 ± 0,1	0,9 ± 0,2	0,6 ± 0,1
PMA (%)	89,3 ± 6,2	78,2 ± 5,8#	81,5 ± 6,5	82,1 ± 6,1
Assessment of dyspnoea based on Borg scale before the test (points)	0	0 ± 0,0	0 ± 0,0	0 ± 0,0
Assessment of dyspnoea based on Borg scale after the test (points)	0–1	2,9 ± 0,4#	2,8 ± 0,4#	2,8 ± 0,4#

Note. # Statistically significant difference compared to the group of healthy individuals ($p < 0.05$).

(48.1 ± 3.5) % to (49.3 ± 3.6) %. The cardiovascular system performance remained unchanged as well: HR/VO_2 from (7.1 ± 3.2) beats/mL/kg to (6.2 ± 2.8) beats/mL/kg, VO_2/HR from (71.3 ± 9.7) % to (72.3 ± 8.2) %. The level of work performed, exercise tolerance and physical activity level remained unchanged: W from (69.5 ± 3.6) % to (70.2 ± 4.1) %, W from (0.8 ± 0.2) W/kg to (0.89 ± 0.1) W/kg., MET from (4.1 ± 1.3) kcal/kg to (4.2 ± 1.4) kcal/kg, RW from (0.9 ± 0.1) W/kg to (0.6 ± 0.2) W/kg, PMA from (78.2 ± 5.8) % to (82.1 ± 6.1) %.

Detailed analysis revealed that patients with bronchial asthma in Group II experienced a decrease in physical activity after exacerbation of the disease. Maximum work performance was achieved due to inefficient functioning

Table 4.

Cardiorespiratory stress test indices in patients with moderate persistent BA in Group II, (M ± m)

Indices	Healthy individuals	Patient Group II		
		Before treatment	Immediately after treatment based on the prototype method	In 3 months after treatment based on the prototype method
	(n = 15)	(n = 15)		
Duration of the 3rd phase of the test (min)	12,92 ± 3,2	6,4 ± 2,2#	8,2 ± 2,1*	8,3 ± 2,4*
$V'O_2$/kg (mL/min/kg)	7,7 ± 1,1	5,6 ± 1,3#	7,2 ± 1,5*	7,3 ± 1,6*
$V'O_2$/kg (%)	82,3 ± 5,6	70,9 ± 2,5#	92,3 ± 4,2*	92,3 ± 2,6*
$V'O_2$ (%)	102,3 ± 5,6	79,3 ± 3,1#	98,3 ± 4,2*	91,6 ± 4,5*
$V'O_{2p}$ (%)	94,3 ± 8,9	77,5 ± 3,1#	85,6 ± 3,5*	86,3 ± 3,2*
$V'O_{2max}$ (%)	99,3 ± 10,3	79,6 ± 7,5#	92,3 ± 6,4*	91,6 ± 5,4*
RER (%)	0,95 ± 0,1	1,03 ± 0,1	1,01 ± 0,1	1,01 ± 0,1
AT (% of $V'O_{2max}$)	65,3 ± 4,3	47,5 ± 3,6	48,3 ± 3,5	49,4 ± 2,9
W (%)	92,9 ± 3,5	69,2 ± 5,2#	92,9 ± 5,2*	92,8 ± 6,1*
W (W/kg)	2,9 ± 1,1	0,7 ± 0,2#	1,2 ± 0,1#*	1,3 ± 0,1#*
W (W)	185,0 ± 6,3	95,6 ± 6,8#	145,3 ± 6,3*	149,2 ± 8,2*
dO_2/dW (mL/min/W)	11,42 ± 1,3	6,9 ± 1,8#	9,5 ± 1,8*	10,3 ± 2,1*
HR/$V'O_2$ (beats/mL/kg)	2,7 ± 1,6	6,9 ± 1,8#	3,5 ± 1,3#*	4,1 ± 1,2#*
$V'O_2$/HR (%)	88,6 ± 9,6	72,6 ± 9,4#	88,1 ± 9,4*	84,6 ± 8,1*
dHR/dO_2 (beats/min/mL)	78,6 ± 4,5	74,6 ± 5,1	78,5 ± 6,5	76,5 ± 5,9
HR (beats/min)	112,5 ± 8,6	125,6,1 ± 7,2#	121,8 ± 7,1#	120,3 ± 6,9#
HR (%)	93,5 ± 9,2	82,1 ± 5,2#	86,9 ± 3,9	87,2 ± 4,2
SpO_2 (%)	98,6 ± 8,2	92,6 ± 8,1	95,9 ± 8,1	97,2 ± 6,8
MET (kcal/kg)	8,4 ± 1,6	4,6 ± 1,8#	7,8 ± 1,5*	7,9 ± 1,5*
RW (W/kg)	1,2 ± 0,1	0,7 ± 0,1	1,1 ± 0,2	1,1 ± 0,1
PMA (%)	89,3 ± 6,2	75,6 ± 5,6#	88,6 ± 6,1*	86,1 ± 6,4
Assessment of dyspnoea based on Borg scale before the test (points)	0	0 ± 0,0	0 ± 0,0	0 ± 0,0
Assessment of dyspnoea based on Borg scale after the test (points)	0–1	3,2 ± 0,4#	2,0 ± 0,4#	1,4 ± 0,4*

Notes: # statistically significant difference compared to the group of healthy individuals ($p < 0.05$); * - statistically significant difference compared to the beginning of treatment ($p < 0.05$).

of the cardiovascular and pulmonary systems at the maximum physical activity. Specifically, BA patients had lower oxygen supply during physical activity than healthy individuals. This was confirmed by reduced ergospirometric indices descriptive of the respiratory system function: $V'O_2$/kg to (70.9 ± 2.5) %, $V'O_2$ to (79.3 ± 3.1) %, $V'O_{2p}$ to (77.5 ± 3.1) %, $V'O_{2max}$ to (79.6 ± 7.5) %, RER to (1.03 ± 0.1) %. There were changes in the cardiovascular system's adaptive capacity to physical activity: the amount of oxygen carried by the heart during maximum physical activity was reduced by restriction of its flow as a result of obstructive changes in the respiratory system, therefore, the amount of oxygen used for work performance was reduced: dHR/dO_2 to (74.6 ± 5.1) %, HR/VO_2 to (6.9 ± 1.8) beats/mL/kg, HR to (125.6 ± 7.2) beats/min and (82.1 ± 5.2) %, VO_2/HR to (72.6 ± 9.4) %. Consequently,

Table 5.

Cardiorespiratory stress test indices in patients with moderate persistent BA in Groups I and II, (M ± m)

Indices	Healthy individuals	Group I – BA patients in 3 months based on the prototype method	Group II – BA patients in 3 months based on the claimed method
		After treatment	
	(n = 15)	(n = 15)	(n = 15)
Duration of the 3rd phase of the test (min)	12,92 ± 3,2	6,4 ± 2,2*	8,2 ± 2,1
$V'O_2$/kg (ml/min/kg)	7,7 ± 1,1	4,2 ± 1,4*	7,2 ± 1,5#
$V'O_2$/kg (ml/min/kg), %	82,3 ± 5,6	74,1 ± 2,2*	92,3 ± 4,2#
$V'O_2$ (%)	102,3 ± 5,6	86,5 ± 3,6*	98,3 ± 4,2#
$V'O_{2p}$ (%)	94,3 ± 8,9	77,9 ± 3,2*	85,6 ± 3,5
$V'O_{2max}$ (%)	99,3 ± 10,3	89,8 ± 2,2*	92,3 ± 6,4
RER (%)	0,95 ± 0,1	1,06 ± 0,1	1,01 ± 0,1
AT (% of $V'O_{2max}$)	65,3 ± 4,3	49,3 ± 3,6	48,3 ± 3,5
W (%)	92,9 ± 3,5	71,5 ± 4,1*	92,9 ± 5,2#
W (W/kg)	2,9 ± 1,1	0,9 ± 0,1*	1,2 ± 0,1#
W (Bt)	185,0 ± 6,3	95,9 ± 7,1*	145,3 ± 6,3#*
dO_2/dW (ml/min/W)	11,42 ± 1,3	7,1 ± 1,6*	9,5 ± 1,8#
dHR/dO_2 (beats/min/ml)	78,6 ± 4,5	78,5 ± 6,5	78,4 ± 6,2
$HR/V'O_2$ (bps/ml/kg)	2,7 ± 1,6	6,9 ± 1,1*	3,5 ± 1,3#*
$V'O_2$/HR (%)	88,6 ± 9,6	68,3 ± 9,2	88,1 ± 9,4#
HR/Vkg (beats/ml/kg)	9,2 ± 3,8	7,9 ± 3,9	8,6 ± 3,1
$V'O_2$/HR (bps/ml/kg)	10,2 ± 2,6	6,8 ± 2,8	10,8 ± 2,4
SpO_2 (%)	98,6 ± 8,2	93,4 ± 8,5	95,9 ± 8,1
MET (kcal/kg)	8,4 ± 1,6	4,7 ± 1,4*	7,8 ± 1,5#
RW (W/kg)	1,2 ± 0,1	0,9 ± 0,2	1,1 ± 0,2
PMA (%)	89,3 ± 6,2	81,5 ± 6,5	88,6 ± 6,1
Assessment of dyspnoea based on Borg scale before the test* (points)	0 ± 0,0	0 ± 0,0	0 ± 0,0
Assessment of dyspnoea based on Borg scale after the test (points)	0–1	2,8 ± 0,4*	2,0 ± 0,4

Notes: # statistically significant difference between groups immediately after treatment ($p < 0.05$); * - statistically significant difference compared to the group of healthy individuals ($p < 0.05$).

exercise tolerance, load level and performed physical activity in patients were reduced: W to (69.2 ± 5.2) %, dO_2/dW to (6.9 ± 1.8) mL/min/W (see Table 4).

After treatment based on the claimed method the patients in this group had significantly normalized indices descriptive of the respiratory system performance: $V'O_2$/kg from (70.9 ± 2.5) % to (92.3 ± 4.2) %, $V'O_2$ from (79.3 ± 3.1) % to (98.3 ± 4.2) %, $V'O_{2p}$ from (77.5 ± 3.1) % to (85.6 ± 3.5) %, $V'O_{2max}$ from (79.6 ± 7.5) % to (92.3 ± 6.4) %. There has been a significant improvement in the following indices descriptive of the cardiovascular system performance: HR/VO_2 from (6.9 ± 1.8) bps/mL/kg to (3.5 ± 1.3) bps/mL/kg, VO_2/HR from (72.6 ± 9.4) % to (88.1 ± 9.4) %. Exercise tolerance indices have improved as well: W from (69.2 ± 5.2) % to (92.9 ± 5.2) %, dO_2/dW from (6.9 ± 1.8) mL/min/W to (9.5 ± 1.8) mL/min/W.

Significant difference persisted in 3 months after administration of the medication based on ginkgolides and bilobalides in the course of the background treatment within the period of remission compared to the beginning of treatment in the following indices: duration of the 3rd phase of the test (6.4 ± 2.2) min to (8.3 ± 2.4) min, $V'O_2$/kg from (70.9 ± 2.5) % to (92.3 ± 2.6) %, $V'O_2$ from (79.3 ± 3.1) % to (91.6 ± 4.5) %, $V'O_{2p}$ from

Table 6.

Cardiorespiratory stress test indices in patients with moderate persistent BA in Groups I and II, (M ± m)

Indices	Healthy individuals	Group I – BA patients based on the prototype method	Group II – BA patients based on the claimed method
		in 3 months after treatment	
	(n = 15)	(n = 15)	(n = 15)
Duration of the 3rd phase of the test (min)	12,92 ± 3,2	6,3 ± 2,2#	8,3 ± 2,4
$V'O_2$/kg (mL/min/kg)	7,7 ± 1,1	3,3 ± 1,6#	7,3 ± 1,6*
$V'O_2$/kg (mL/min/kg), %	82,3 ± 5,6	75,3 ± 2,4#	92,3 ± 2,6*
$V'O_2$ (%)	102,3 ± 5,6	85,1 ± 4,1#	91,6 ± 4,5
$V'O_{2p}$ (%)	94,3 ± 8,9	78,2 ± 3,6#	86,3 ± 3,2
$V'O_{2max}$ (%)	99,3 ± 10,3	88,2 ± 2,4#	91,6 ± 5,4
RER	0,95 ± 0,1	1,01 ± 0,1	1,01 ± 0,1
BR (%)	88,1 ± 6,2	73,2 ± 2,3#	79,6 ± 5,2
AT (%)	49,65 ± 4,3	48,9 ± 3,2	49,4 ± 2,9
SVc (mL)	8,4 ± 1,5	7,2 ± 1,4	7,6 ± 1,4
W (%)	92,9 ± 3,5	70,2 ± 4,1#	92,8 ± 6,1*
W (W/kg)	2,9 ± 1,1	0,89 ± 0,1#	1,3 ± 0,1*
W (W)	185,0 ± 6,3	94,5 ± 8,1#	149,2 ± 8,2*
dO_2/dW (mL/min/W)	11,42 ± 1,3	8,2 ± 1,8#	10,3 ± 2,1
dHR/dO_2 (beats/min/mL)	78,6 ± 4,5	76,5 ± 5,9	79,6 ± 5,2
HR/$V'O_2$ (beats/mL/kg)	2,7 ± 1,6	6,2 ± 2,8#	4,1 ± 1,2#
$V'O_2$/HR (beats/mL/kg)	10,2 ± 2,6	6,9 ± 2,2	10,4 ± 2,1
$V'O_2$/HR (%)	88,6 ± 9,6	72,3 ± 8,2#	84,6 ± 8,1
MET (kcal/kg)	8,4 ± 1,6	4,2 ± 1,2#	7,9 ± 1,5*
RW (W/kg)	1,2 ± 0,1	0,6 ± 0,1	1,1 ± 0,1
PMA (%)	89,3 ± 6,2	82,1 ± 6,1	86,1 ± 6,4
Assessment of dyspnoea based on Borg scale before the test* (points)	0 ± 0,0	0 ± 0,0	0 ± 0,0
Assessment of dyspnoea based on Borg scale after the test (points)	0–1	2,8 ± 0,4#	1,4 ± 0,4*

Notes: * statistically significant difference between groups immediately after treatment ($p < 0.05$); # statistically significant difference compared to the group of healthy individuals ($p < 0.05$).

(77.56 ± 3.1) % to (86.3 ± 3.2) %, $V'O_{2max}$ from (79.6 ± 7.5) % to (91.6 ± 5.4) %. Significant difference persisted in the cardio-vascular system performance indices compared to the beginning of treatment: HR/VO_2 from (6.9 ± 1.8) beats/ml/kg to (10.3 ± 2.1) beats/mL/kg, VO_2/HR from (72.6 ± 9.4) % to (84.6 ± 8.1) %, MET from (4.6 ± 1.8) kcal/kg to (7.9 ± 1.5) kcal/kg. Significant difference also persisted in work performed indices compared to the beginning of treatment: W from (69.2 ± 5.2) % to (92.8 ± 6.1) %, dO_2/dW from (6.9 ± 1.8) mL/min/W to (10.3 ± 2.1) mL/min/W. The positive tendency to normalization in comparison with the beginning of treatment persisted in the rest of cardiovascular indices.

Significant difference in measured outcome was established by comparison of indices in both groups. Specifically, there was significant difference in the pulmonary system performance indices: $V'O_2$/kg, $V'O_2$ (see Table 5).

Significant difference was observed in the cardio-vascular system performance indices: HR/VO_2 to (6.9 ± 1.1) beats/mL/kg in Group I and (3.5 ± 1.3) beats/mL/kg in Group II. VO_2/HR to (68.3 ± 9.2) % in Group I and (88.1 ± 9.4) %, MET to (4.7 ± 1.4) kcal/kg in Group I and

(7.8 ± 1.5) kcal/kg. The indices descriptive of exercise tolerance, level of work performed and patient's activity were significantly different as well: W to (71.5 ± 4.1) % in Group I and (92.9 ± 5.2) % in Group II. dO_2/dW to (7.1 ± 1.6) mL/min/W in Group I and (9.5 ± 1.8) mL/min/W. Yet, in Group I, which received treatment based on the prototype method, there was a significant difference compared to the group of healthy individuals in the following indices: the duration of the 3rd phase of the test, $V'O_2/kg$, $V'O_2$, $V'O_{2p}$, $V'O_{2max}$, $V'O_2$ (V-slope), $V'CO_2$ (V-slope), BR, W, dO_2/dW, HR/VO2, MET. The significant difference in the group treated based on the claimed method compared to the group of healthy individuals was observed in the following indices: W, HR/VO_2 (see Table 6).

In 3 months after the received treatment, significant difference was observed between the groups in the following indices: $V'O_2/kg$ to (75.3 ± 2.4) % in Group I and to (92.3 ± 2.6) % in Group II, W to (70.2 ± 4.1) % in Group I and to (92.8 ± 6.1) % in Group II. SBP to (181.0 ± 7.2) mm Hg and (158.2 ± 8.6) mm Hg. MET to (4.2 ± 1.2) kcal/kg in Group I, to (7.9 ± 1.5) kcal/kg in Group II. In patients with bronchial asthma in Group I, who were treated based on the prototype method, in 3 months after the received treatment the significant difference persisted compared to the group of healthy individuals in terms of efficiency of the pulmonary and cardiovascular systems performance: the duration of the 3rd phase of the test, $V'O_2/kg$, $V'O_2$, $V'O_{2p}$, $V'O_{2max}$, $V'O_2$ (V-slope), $V'CO_2$ (V-slope), BR, W, dO_2/dW, HR/VO2, HR, VO_2/HR, SBP, DBP, MET.

In patients in Group II, who were treated with the medicinal product based on ginkgolides and bilobalides against the background of standard treatment during the period of remission, in 3 months after treatment the indices of cardiorespiratory test did not differ from those in the group of healthy individuals. The difference was only in the HR/VO_2 index, which is representative of the amount of oxygen carried due to cardiac function at the maximum physical activity.

Thus, administration of the medicinal product containing ginkgolides and bilobalides in the course of the background treatment within the period of remission of bronchial asthma with a view to prevent the decline of physical working capacity in these patients makes it possible to:

- increase metabolic equivalent of task (MET) and level of work performed by an average of 32 %;
- improve patient's muscle activity, level of accomplished load and physical activity by 37 %;
- increase oxygen cost of work performed by an average of 27 %
- improve average oxygen consumption (O_2) effectiveness indices: $V'O_2$ by 36 % $V'O_{2p}$ by 28 %, maximum oxygen consumption at the peak load ($V'O_{2max}$) by 16 %;
- reduce hyperventilation, improve effectiveness of cardiovascular system performance by increasing oxygen pulse (VO_2/HR) by 24 %.

The proposed method can be recommended for widespread introduction into clinical practice in pulmonary institutions.

Список літератури

1. Фещенко, Ю. И. Современная стратегия ведения бронхиальной астмы [Текст] / Ю. И. Фещенко, Л. А. Яшина // Астма та алергія. – 2007. – № 3–4. – С. 8–11.
2. Фещенко, Ю. І. Особливості функціонального стану серцево-судинної системи у хворих на бронхіальну астму [Текст] / Ю. І. Фещенко, Л. М. Курик, О. А. Канарський // Матеріали міжнародної науково-практичної конференції на тему «Медична наука та практика» (м. Київ, 7–8 лютого 2014). – 2014. – № 1. – С. 48–52.
3. Feshchenko, Yu. I. Physical activity of patients suffering from a mild form of bronchial asthma [Text] / Y. I. Feshchenko, N. A. Prymushko, L. M. Kuryk, V. V. Kuts, O. I. Adamchuk, I. P. Turchyna, O. A. Kanarskyi, O. I. Krylach // Asthma and allergy. – 2014. – № 1. – P. 5–12.
4. Efficient Extraction of Ginkgolides and Bilobalides [Text] / K. Nakanishi, [et al.] // J. Nat. Prod. – 2011. – № 5. – P. 33–45.
5. Summative Interaction Summative Interaction between Astaxanthin, Ginkgobiloba Extract (EGb761) and Vitamin C in Suppression of Respiratory Inflammation: A Comparison with Ibuprofen [Text] / D. D. Haines, [et al.] // Phytotherapy Research. – 2011. – № 25. – P. 128–136.
6. Efficient Extraction of Ginkgolides and Bilobalides from Ginkgo biloba leaves [Text] / D. Lichtblau, [et al.] // J. Nat. Prod. – 2002 – № 65. – P. 150–154.
7. Montoro, P. Ginkgo biloba extracts: A Review of the Pharmacokinetics of the Active Ingredients. Institute of Pharmaceutical Chemistry. [Електронный ресурс]. – Режим доступу http://link.springer.com/html.
8. Van Beek, T. A. Chemical analysis and quality control of Ginkgo biloba leaves, extracts, and phyto pharmaceuticals [Text] / T. A. Van Beek // Journal of Chromatography. – 2009. –№ 11. – P. 2002–2032.
9. Cornelia, A. Role of Ginkgo biloba In Suppression Of Asthma [Text] / A. Cornelia // Clinical Pharmacokinetics. – 2013. – № 52. – P. 545–549.
10. Pharmaceutical Benefits of Ginkgo Biloba (Tree Of Life) [Text] / G. Singh1, [et al.] // J of Biomedical and Pharmaceutical Research. – 2013. – № 2. – P. 15–21.

References

1. Feshhenko YuI, Yashina LA. Sovremennaja strategija vedenija bronhial'noj astmy (Current management of bronchial asthma). Astma ta alergija. 2007;3–4: 8 –11.
2. Feshchenko YuI, Kurik LM, Kanars'kiy OA. Osoblivosti funktsional'nogo stanu sertsevosudinnoї sistemi u khvorikh na bronkhial'nu astmu (Features of the functional state of the cardiovascular system in patients with asthma). Materiali mizhnarodnoї naukovopraktichnoї konferentsiї na temu «Medichna nauka ta praktika»;2014 Nov 7–8 Kyiv;1:48–52.
3. Feshchenko YuI, Prymushko NA, Kuryk LM, Kuts VV, Adamchuk OI, Turchyna IP, Kanarskyi OA, Krylach OI. Physical activity of patients suffering from a mild form of bronchial asthma. Asthma and allergy. 2014;1:5–12.
4. Nakanishi K, et al. Efficient Extraction of Ginkgolides and Bilobalides. J Nat Prod. 2011;5:33–45.
5. Haines DD, et al. Summative Interaction Summative Interaction between Astaxanthin, Ginkgobiloba Extract (EGb761) and Vitamin C in Suppression of Respiratory Inflammation: A Comparison with Ibuprofen. Phytotherapy Research. 2011;25:128–136.
6. Lichtblau D, et al. Efficient Extraction of Ginkgolides and Bilobalides from Ginkgo biloba leaves. J Nat Prod. 2002;65:150–154.
7. Montoro P. Ginkgo biloba extracts: A Review of the Pharmacokinetics of the Active Ingredients. Institute of Pharmaceutical Chemistry. Available from: http://link.springer.com/html.
8. Van Beek TA. Chemical analysis and quality control of Ginkgo biloba leaves, extracts, and phyto pharmaceuticals. Journal of Chromatography. 2009;11:2002–2032.
9. Cornelia A. Role of Ginkgo biloba In Suppression Of Asthma. Clinical Pharmacokinetics. 2013;52:545–549.
10. Singh G, et al. Pharmaceutical Benefits of Ginkgo Biloba (Tree Of Life). J of Biomedical and Pharmaceutical Research. 2013;2:15–21.
11. Singh M, et al. Phytopharmacological Potential of Ginkgo biloba: A Review. J of Pharmacy Research 2012;5:28–35.

11. Phyto-pharmacological Potential of Ginkgo biloba: A Review [Text] / M. Singh, [et al.] // J of Pharmacy Research 2012. – № 5. – P. 28–35.

12. Research progress on polysaccharides from Ginkgo biloba [Text] / L. He, [et al.] // Journal of Medicinal Plants Research.– 2012. – № 6. – P. 171–176.

13. Ginkgo extractEGb761 confers neuroprotection by reduction of glutamate release in ischemic brain, [Text] / A. Mdzinarishvili, [et al.] // Journal of Pharmacy and Pharmaceutical Sciences. – 2012. – № 5. – P. 94–102.

14. Про затвердження клінічних протоколів надання медичної допомоги за спеціальністю «Пульмонологія» [Текст]: Наказ МОЗ України № 128 від 19.03.2007 р. – Київ, 2007. – 146 с. On approval of clinical protocols of medical care in the specialty «Pulmonology». (Decree of MOH of Ukraine № 128 from 19.03.2007)

15. Фещенко, Ю. И. Особенности бронхиальной астмы у больных с метаболическим синдромом [Текст] / Ю. И. Фещенко, Л. А. Яшина // Здоров'я України. – 2014. – № 2 (26). – С. 6–8.

16. Kuryk, L. M. Efficiency ginkgolides and bilobalides in complex correction of erythrocyte homeostasis in asthma patients [Text] / L. M. Kuryk // Астма та алергія. – 2014. – № 2. – С. 12–18.

17. Курик, Л. М. Вплив гінкголідів та білобалідів на реологічну властивість крові у хворих на бронхіальну астму [Текст] / Л. М. Курик, О. І. Адамчук, О. А. Канарський // Матеріали міжнародної науково-практичної конференції на тему «Забезпечення здоров'я нації та здоров'я особистості як пріоритетна функція держави» (м. Одеса, 21–22 лютого 2014). – 2014. – № 1. – С. 40–44.

18. Курик, Л. М. Клініко-функціональна ефективність препаратів, до складу яких входять гінкголіди та білобаліди у комплексному лікуванні хворих на бронхіальну астму [Текст] / Л. М. Курик, О. А. Канарський, О. І. Крилач // Матеріали міжнародної науково-практичної конференції на тему «Перспективні напрямки розвитку сучасних медичних та фармацевтичних наук» (м. Дніпропетровськ, 14–15 березня 2014). – 2014. – № 1. – С. 53–57.

19. Бабич, П. Н. Применение современных статистических методов в практике клинических исследований. Сообщение третье. Отношение шансов: понятие, вычисление, интерпретация [Текст] / П. Н. Бабич, А. В. Чубенко, С. Н. Лапач // Український медичний часопис. – 2005. – № 2. – С. 113–119.

20. Лапач, С. Н. Статистические методы в медико-биологических исследованиях с использованием Excel [Текст] / С. Н. Лапач, А. В. Чубенко, П. Н. Бабич. – К.: Морион, 2001. – 320 с.

12 He L, et al. Research progress on polysaccharides from Ginkgo biloba. Journal of Medicinal Plants Research.2012;6:P. 171–176.

13. Mdzinarishvili A, et al. Ginkgo extractEGb761 confers neuroprotection by reduction of glutamate release in ischemic brain. Journal of Pharmacy and Pharmaceutical Sciences. 2012;5:94–102.

14. Nakaz MOZ Ukraïni № 128 vid 19.03.2007r. Pro zatverdzhennya klinichnikh protokoliv nadannya medichnoï dopomogi za spetsial'nistyu «Pul'monologiya» (Decree of MOH of Ukraine № 128 from 19.03.2007. On approval of clinical protocols of medical care in the specialty «Pulmonology». Kyiv: 2007. 146 p.

15. Feshchenko YuI, Yashina LA. Osobennosti bronkhial'noy astmy u bol'nykh s metabolicheskim sindromom (Features of asthma in patients with metabolic syndrome). Zdorov'ya Ukraïni. 2014:2 (26):6–8.

16. Kuryk L. M. Efficiency ginkgolides and bilobalides in complex correction of erythrocyte homeostasis in asthma patients. Астма та алергія. 2014;2:12–18.

17. Kurik LM, Adamchuk OI, Kanars'kiy OA. Vpliv ginkgolidiv ta bilobalidiv na reologichnu vlastivist' krovi u khvorikh na bronkhial'nu astmu (Impact of ginkgolides and bilobalidiv on the rheological properties of blood in patients with asthma). Materiali mizhnarodnoï naukovopraktichnoï konferentsiï na temu «Zabezpechennya zdorov'ya natsiï ta zdorov'ya osobistosti yak prioritetna funktsiya derzhavi»;2014 Febr 21–22 Odesa;1:40–44.

18. Kurik LM, Kanars'kiy OA, Krilach OI. Kliniko-funktsional'na efektivnist' preparativ, do skladu yakikh vkhodyat' ginkgolidi ta bilobalidi u kompleksnomu likuvanni khvorikh na bronkhial'nu astmu (Clinical and functional efficacy of drugs, which include ginkgolides and bilobalidy in treatment of patients with asthma). Materiali mizhnarodnoï naukovopraktichnoï konferentsiï na temu «Perspektivni napryamki rozvitku suchasnikh medichnikh ta farmatsevtichnikh nauk»;2014 Mar 14–15 Dnipro;1:53–57.

19. Babich PN, Chubenko AV, Lapach SN. Primenenie sovremennyy statisticheskikh metodov v praktike klinicheskikh issledovaniy. Soobshchenie tret'e. Otnoshenie shansov: ponyatie, vychislenie, interpretatsiya (The use of modern statistical methods in the practice of clinical research. Message three. The odds ratio: definition, calculation, interpretation). Ukraïns'kiy medichniy chasopis. 2005;2:113–119.

20. Lapach SN, Chubenko AV, Babich PN. Statisticheskie metody v medikobiologicheskikh issledovaniyakh s ispol'zovaniem Excel (Statistical methods in biomedical research using Excel). Kyiv: Morion;2001. 320 p.