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РЕСПИРАТОРНАЯ РЕАБИЛИТАЦИЯ ПОСТ-COVID-19 ПАЦИЕНТОВ.

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Respiratory Rehabilitation for Post-Covid-19 Patients

Резюме

В представленном клиническом обзоре нами оценены возможности лекарственных и немедикаментозных стратегий устранения и предотвращения патофизиологических изменений респираторной системы пост-COVID-19 пациентов. Предлагаются актуальные реабилитационные алгоритмы, основанные на оценке тяжести клинических проявлений новой коронавирусной инфекции (COVID-19), возможностях реабилитационных методик и персональной приверженности пациента к их выполнению.

Ключевые слова: *дыхательная гимнастика, экспираторные дыхательные тренажёры, мотивирующие вдох спирометры, интрапульмональная перкуссионная вентиляция лёгких, откашливатели, CPAP-терапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

In the presented clinical review, we evaluated the possibilities of drug and non-drug strategies for eliminating and preventing pathophysiological changes in the respiratory system of post-COVID-19 patients. We offer up-to-date rehabilitation algorithms based on the assessment of the severity of clinical manifestations of COVID-19, the possibilities of rehabilitation techniques and the patient's personal compliance with their implementation.

Key words: *breathing exercises, expiratory breathing simulators, incentive spirometer, intrapulmonary percussion ventilation, coughing devices, CPAP, LTOT, oPEP*

Conflict of interest

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ACBTh — active cycle of breathing technique with huffing, BiPAP — bi-level positive airway pressure ventilation, CPAP — continuous positive airway pressure ventilation, FiO2 — fraction of inspired oxygen, IPV — intrapulmonary percussive ventilation, InS — incentive spirometer, LAAC — long-acting anticholinergics, LABA — long-acting b2-agonists, LTOT — long-term oxygen therapy, MI-E — mechanical insufflation/exsufflation devices, oPEP — oscillatory positive expiratory pressure breathing simulator, PAH — pulmonary arterial hypertension, PEEP — techniques with positive end-expiratory pressure, PR — pulmonary rehabilitation, RF — respiratory failure, RR — respiratory rate, SpO2 — arterial oxygen saturation

Introduction

The rehabilitation of post-COVID-19 patients should be comprehensive and take into consideration the following [1]:

- pathological changes in organs and systems, whose severity is determined by disease severity and the extent of tissue damage;
- iatrogenic lesions associated with side effects of medications (for example, cardiotoxicity, hepatotoxicity) and medical procedures (for example, tracheostomy, intubation);
- concomitant diseases (comorbidities);
- psychological constitution of the patient.

Therefore, it is almost impossible to develop a universal rehabilitation regimen. A patient-specific syndromic and pathogenetic approach that provides the maximum effectiveness of each rehabilitation technique depending on pathological changes present in the patient is preferable [2]. Obviously, pulmonary rehabilitation (PR) methods should be modified for such patients. Pulmonary rehabilitation should be understood as a complex intervention based on a thorough assessment of the patient's condition, followed by selecting personalized treatment that allows the patient [3]:

- to keep fit (physiotherapy);
- to change lifestyle and behavior through learning in order to improve physical and psychological state;
- to maintain commitment to healthy behavior.

There are two main types of PR: 1) pulmonary/drainage methods (PDM); 2) respiratory/ventilation methods (RVM). The former — PDM — are aimed at restoring mucociliary clearance and are based on: extrapulmonary vibration exposure and postural drainage; intrapulmonary percussion; optimizing coughing (huffing) and breathing practices; vacuum massage and bronchoalveolar lavage. The latter — RVM — are aimed at strengthening respiratory muscles and normalizing gas exchange and are based on: respiratory muscle training; optimization of phases of the breathing cycle; improvement of mechanical properties of lungs, normalization of standard lung volumes [4].

The development of rehabilitation programs should be based on the indications/contraindications of specific techniques, their possible interaction and avoiding excessive drug treatment. The main pathological changes (general and respiratory) in patients after COVID-19 are listed below, in relation to possible rehabilitation techniques (Table 1).

In most cases, COVID-19 patients have multiple lesions, which is why they need additional laboratory and diagnostic tests at the rehabilitation stage, in addition to medical history and clinical examination [5].

1. PULMONARY/DRAINAGE REHABILITATION METHODS

The choice of rehabilitation methods should be based on present indications/contraindications; comorbidities; clinical evaluation of the positive/negative effects of techniques. More detailed mechanisms of action, indications and contraindications are presented in the clinical recommendations for the medical rehabilitation of COVID-19 patients [6].

1.1. Physical activity

Objective: stimulation of blood/lymph circulation in muscles. *Action:* long aerobic exercises with light loads and low respiratory rate (RR) (not higher than 100/min). *Preferred types of activity*: Nordic walking, rowing machine, breaststroke swimming.

1.2. Chest massage

Objective: stimulation of blood/lymph circulation in muscles. *Action:* massage of the neck and collar zone and chest. *Preferred types of activity*: compression and vibration massage in combination with postural drainage.

1.3. Exercises with positive end-expiratory pressure

Objective: increasing the uniformity of lung ventilation. *Mechanism of action:* positive air pressure and high airflow velocity during forced expiratory maneuvers in cases of airway instability are accompanied by dynamic compression of airways (expiratory collapse, EC), which causes partial emptying of alveoli and mucus retention in small bronchi. To prevent EC, if there are no expiratory simulators, the simplest respiratory techniques can be used to create positive end-expiratory pressure (PEEP). For this purpose, inflatable low-resistance elastic items (condoms, medical gloves, balloons) are often used. It should be noted that the patient should perform the exhalation maneuver without significant

Table 1. *Pathological changes and possible rehabilitation methods*

Parameter	Rehabilitation techniques
General pathological changes	
Asthenic syndrome	Halotherapy, psychotherapy, therapeutic nutrition, vitamins, magnesium preparations, thyroxine replacement therapy
Muscle weakness	Massage, light physical training, thyroxine replacement therapy
Subfebrile condition	Paracetamol, low doses of steroid hormones while maintaining radiological manifestations of interstitial lung damage, antibiotics for confirmed bacterial infection
Depression	Halotherapy, psychotherapy, antidepressants
Obstructive sleep apnea	CPAP therapy
Sleep disorder	CPAP therapy, sedatives, sleeping pills
Respiratory disorders	
Hypoxemia	LTOT, InS, oPEP, IPV, CPAP therapy
Hypoxemia with hypercapnia	BiPAP therapy
Pulmonary hypertension (PH)	Drug therapy according to indications, mild to moderate PH: LTOT, oPEP, IPV
Bronchoobstructive syndrome	Inhaled bronchodilators (LABA/LAMA), halotherapy, IPV, CAD
Difficulty in expectoration	Mucolytics, halotherapy, IPV, CAD, postural drainage, chest vibration massage, ACB-H
Shortness of breath not associated with bronchial obstruction *(exclude manifestations of heart failure)*	Breathing exercises of full breath (pranayama), InS, breathing exercises with PEEP, oPEP, IPV, halotherapy, psychotherapy
Irregular ventilation and ventilation-perfusion disorders	Complete breathing exercises (pranayama), ACB-H, InS, breathing exercises with PEEP, oPEP, IPV

Note: CPAP — continuous positive airway pressure; LTOT — long-term oxygen therapy; InS– incentive spirometer; oPEP — oscillating positive expiratory pressure device; IPV — intrapulmonary percussive ventilation; BiPAP — bilevel positive airway pressure; LABA — long-acting b2 agonists; LAMA — long-acting M-anticholinergic agent; CAD — cough assist devices (insufflation/exsufflation); ACB-H — active cyclic breathing with huffing (rapid exhalation maneuver with clearing of throat); PEEP — positive end expiratory pressure

engagement of accessory respiratory muscles due to the risk of pulmonary barotrauma. In addition, uncontrolled resistance and its significant variation during the exhalation process are considered shortcomings of this technique. The effectiveness of such breathing exercises remains doubtful [7].

1.4. Respiratory gymnastics and postural drainage

Objective: stimulation of mucociliary and cough clearance in cases of a large amount of hard-to-remove sputum. *Mechanism of action:* these procedures are required in patients with destructive processes in lungs or with traction bronchiectasis with severe pneumosclerosis. A set of respiratory exercises is determined by the localization of the purulent production process. When performing drainage exercises, the pulmonary zone with a lesion should be located above the tracheal bifurcation, allowing to create a fluid outflow from the affected bronchi/cavities (postural drainage). Preliminary applications of warming materials (therapeutic mud, paraffin, ozokerite) and exposure of lungs to decimetric electromagnetic waves that dilute sputum and stimulate peripheral hemodynamics can increase the effectiveness of postural drainage [8].

1.5. Sound respiratory gymnastics

Objective: respiratory muscle training, increasing the uniformity of lung ventilation. *Mechanism of action:* exercises with the pronunciation of certain sounds and/or their combinations in a strictly defined manner transmits the vibration of vocal cords to the smooth muscles of bronchi/lungs and chest, causing the relaxation of spasmodic muscles. Airflow strength when pronouncing certain sounds depends on the frequency of vibration. This technique can be used to train respiratory muscles, and therefore, the diaphragm (the largest respiratory muscle) [8].

1.6. Breathing gymnastics (pranayama)

Objective: increasing the uniformity of lung ventilation, developing the correct breathing pattern. *Mechanism of action:* taking a "full breath" combined with the development of the correct breathing pattern (category of yoga breathing exercise "pranayama"). This exercise is based on consistent and maximum ventilation of different lung sections with the possible normalization of the ventilation/perfusion ratio. *Preferred type of exercise* [8, 9]:

1. Starting position — sitting on a chair with back straight and resting on the chair back, hands on knees, head not bowed ("proud posture").
2. Before starting this exercise, relax the chest by lifting shoulders and then lowering them relaxed backward.
3. Breathing in through the nose with a slightly strained nasopharynx (breathing in as if sniffing).
4. During the first phase of inspiration, the lower parts of lungs are ventilated. To this end, the anterior abdominal wall moves forward when the diaphragm is contracted and lowered.

5. Then the upper parts of the lungs are ventilated smoothly and without delay. To this end, the chest expands due to the work of the intercostal muscles in the second phase of inspiration. Maximum inspiration, if possible, should be carried out without noticeable efforts of accessory respiratory muscles.
6. Exhalation should be not forced but passive, using the weight of the chest, through pursed or puckered lips ("punctured tire" effect).
7. Make 20–30 breaths three times a day.

1.7. Forced expiration technique with huffing

Objective: increasing the uniformity of lung ventilation, stimulation of cough clearance with hard-to-remove sputum, re-expansion of atelectasis. *Preferred type of exercise* [10]:

1. After 3–5 slow deep breathing movements, take a deep breath through the nose. Using diaphragmatic breathing, breathe out through closed lips (single maneuver).
2. Take a deep breath and hold the breath for 1–3 seconds; expire a medium/low lung volume (to remove secretion from the peripheral part of the bronchial tree).
3. Take a normal breath; then, during exhalation, squeeze the air out of the lungs using abdominal and chest muscles, with an opened glottis, pronouncing "ha-af-fa" sound (sounds like a forced breath). Repeat several times (3–4 times).
4. When feeling that there is secretion in the upper respiratory tract, expire a large/medium lung volume (to remove sputum from proximal bronchi). Repeat this maneuver 2–3 times.
5. Perform several relaxation diaphragmatic maneuvers before the next cough effort.

1.8. Active cycle of breathing technique (ACBT)

Objective: increasing the uniformity of lung ventilation, stimulation of cough clearance with hard-to-remove sputum, re-expansion of atelectasis. *Mechanism of action*: based on the combination of three breathing techniques: breathing control, chest expansion control, forced expiratory method with huffing (Fig. 1) [10, 11].

Breathing Control (BC) is the technique of the diaphragmatic control of calm inspiration/expiration to relax the respiratory tract and muscles. When performing BC, the patient controls the upper part of the chest, breathes with his/her usual tidal volume (TV) with the usual respiratory rate (RR). This technique is considered effective with the subjective sensation of the so-called "distention" around the waist during inspiration associated with a falling diaphragm; this sensation disappears when expiring. BC is essentially the connective basis between active cycles of breathing techniques (ACBT).

Chest expansion control (CEC) is the technique of slow deep/full inspiration with brief breath-holding (1–2 seconds) and subsequent resting expiration. CEC allows air to spread to the most distal parts of the patient's bronchial tree. In addition, CEC increases airflow in the peripheral respiratory tract (RT), which significantly increases air volume for mobilizing tracheobronchial secretion. Performing 3–4 cycles of CEC is considered sufficient — it prevents muscle fatigue and hyperventilation.

Forced expiratory technique with huffing (FET-H) is a technique of two consecutive forced expirations with an opened glottis and mouth and with an "HA-A-A-A-FA" sound (hence the name "huffing"). FET-H can cause expectoration (coughing up); therefore, this technique usually completes the cycle of breathing techniques (Fig. 1).

Patients with hypersecretion or production of a large volume of sputum with no bronchial hyperreactivity, atelectasis, significant mucoid impactions/occlusions of small bronchi should perform a cycle of BC + CEC + BC + 2-FET-H, repeat 4–6 times in the course of ACBT. Patients with bronchospasm/airway obstruction are recommended to perform more BC repetitions (> 4/cycle), while patients with atelectasis or restrictive pathology (lung compression) require more CEC repetitions (> 6/cycle). An obvious measure of the effectiveness of ACBT is the improvement of lung auscultatory parameters. However, the advantages of this strategy (ACBT) in various groups of patients with respiratory pathology remain difficult to understand [11].

2. DRAINAGE REHABILITATION METHODS WITH SIMULATORS

In some cases, rehabilitation measures, especially those associated with the restoration of drainage function, are impossible without special medical devices — breathing simulators (BS) — that can significantly increase the effectiveness of the procedure and the patient's compliance with it. The most common BS can be divided into: 1) incentive (inspiration inducing) spirometers (InS); 2) positive end-expiratory pressure devices (PEEP/PEP); 3) oscillating positive expiratory pressure devices (oPEP) [13].

2.1. Hyperinflation (volume expanding) therapy with InS

Intermittent pressure hyperinflation (volume expanding) therapy (IPHT) is a variant of the physiotherapeutic effect on the lungs by inspiration of an excessive volume / with excessive pressure that re-expands atelectases and trains the patient's inspiratory muscles. In practice, IPHT is impossible without inspiratory air control devices referred to as "incentive spirometers" (InS). InS devices produce an effect on the distal parts

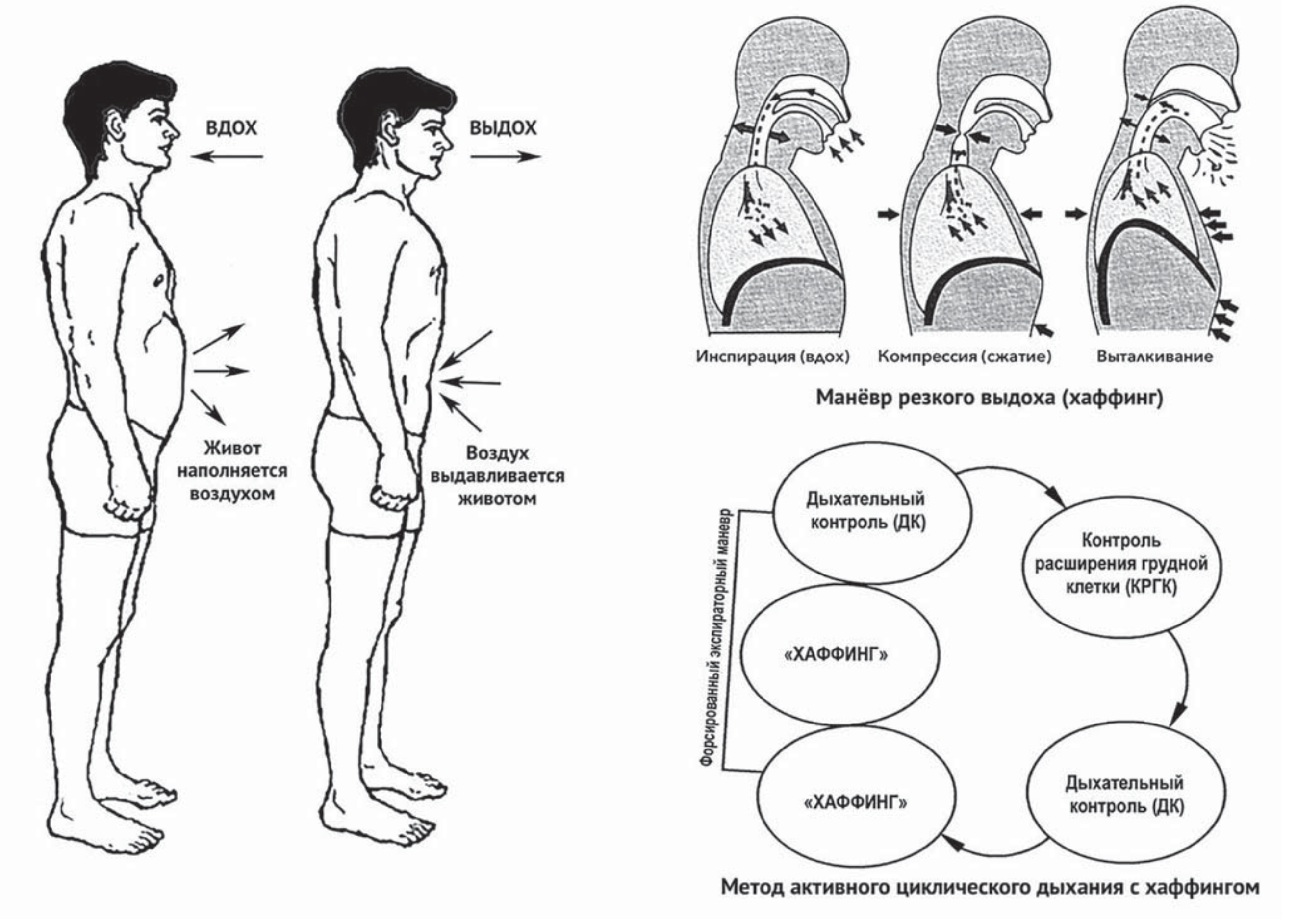

Figure 1. *Schematic representation of active cycle of breathing technique with huffing. The explanation in the text (adapted from: Fink JB. Respir Care. 2007; 52(9): 1210–21, [12])*

of the patient's lung apparatus and are divided into the following types: 1) with inhaled flow control (flow InS or FInS); 2) with inhaled volume control (volume InS or VInS) [14].

Treatment objective: respiratory muscle training, increasing the uniformity of lung ventilation, recruitment of poorly ventilated areas. Mechanism of action: based on a combination of re-expansion/opening of narrowed/obstructed airways, increased collateral ventilation, and "alveoli opening" time. IPHT therapy primarily allows to eliminate "air trapping", prevent/re-expand pulmonary atelectasis, and mobilize/expectorate accumulated tracheobronchial secretion. In other words, IPHT therapy is associated with a "load" that stimulates an increase in O_2 and CO_2 gas exchange, which increases "alveolar stratification" (diffusion changes in gas/blood phase) and perfusion (blood flow). In addition, increased collateral ventilation/blood flow will significantly reduce alveolar collapses and increase the duration of "alveoli opening". Such an effect is called a "recruitment maneuver" — a deliberate measure that increases dynamic transpulmonary pressure for the complete opening of unstable/airless (collapsed) alveoli [15].

2.2. Positive pressure therapy with PEEP/PEP simulators

Respiratory support with positive airway pressure should be performed in patients with instability/variability of the airway lumen. It is most often performed with the help of positive end-expiratory pressure (PEEP/PEP) devices. Objective: mobilization and evacuation of tracheobronchial secretion by increasing intrathoracic pressure of distal lungs; increasing collateral ventilation and training of respiratory muscles. Mechanism of action: based on physiological effects of elimination of alveolar collapse, longer "alveoli opening" time, increased collateral ventilation/blood flow. The following are the main indications for PEEP/PEP therapy [17]:

- recurrent sputum not responding to spontaneous cough;
- pulmonary diseases with hypersecretion/secretion accumulation, previously successfully treated by postural drainage technique (including chest procedures);
- air trapping and lung atelectasis that should be eliminated;

- optimization of aerosol distribution during bronchodilator therapy.

PEEP/PEP devices can be delivered as separate modules or as nebulizer valves. The latter allow to perform PEEP/PEP therapy simultaneously with drug delivery. In such cases, the PEEP/PEP valve generates high expiratory pressure of 20–90 mbar. Obviously, such pressure significantly limits/trains expiration; this determines a good combination of PEEP/PEP valves with small volume mesh nebulizers. If low pressure (10–20 mbar) is to be used in patients with impaired "respiratory drive" (respiratory failure with a normocapnic pattern), separate modules with a PEEP/PEP pressure gauge should be used, which can be connected with a face unit (mask or mouthpiece) [10].

2.3. Positive pressure therapy with oPEP simulators

Positive pressure respiratory support can be combined with oscillatory effects on the lung component. It is most often performed with the help of oscillatory positive expiratory pressure (oPEP) devices. *Objective:* mobilization and evacuation of tracheobronchial secretion by increasing intrathoracic pressure of distal lungs; increasing collateral ventilation and training of respiratory muscles, cough stimulation. *Mechanism of action*: based on physiological effects of expiration against positive pressure with rapidly changing/oscillating resistance; it allows to stabilize/open airways (expansion effect), eliminate air trappings (expansion effect), dilute and mobilize secretion (thixotropic effect), stimulate mucociliary clearance (resonant frequency effect with the ciliary epithelium at a frequency of 12–15 Hz). oPEP therapy is highly safe since small portions of air cannot dramatically increase pressure and cause barotrauma. In addition, the operating pressure of oPEP therapy is considered low, in the range of 15–20 mbar. The main indications for oPEP therapy are the same as those for PEEP/PEP therapy [18]. oPEP devices can be made as separate modules connected with the endotracheal or tracheostomy tube. *The following method is preferred* after basic treatment procedures (basic therapy) or additional bronchodilator therapy [10]:

1. The patient in the sitting position, with a straight back and head stretched up, performs the relaxed breathing control technique.
2. The patient makes full inspirations (2–3 times deeper than usual), with breath holding at maximum inspiration for 2–3 seconds; at least 3 repetitions should be done.
3. The patient breathes in and out with effort (expiration flow is 2–3 times more intense than usual) through the mouthpiece of the flutter (oPEP device), for more than 6 seconds, avoiding unproductive cough at the beginning of expiration; the oPEP device should be placed horizontally to achieve the most effective vibrations; 15–20 repetitions should be done.
4. A "forced expiratory technique with huffing" (FET-H) or similar is performed to stimulate cough and expectoration; at least 2 repetitions should be done.

3. MECHANICAL VENTILATION METHODS FOR REHABILITATION

3.1. Intrapulmonary percussive ventilation (IPPV)

Intrapulmonary percussive ventilation (IPPV) is a hybrid method of high-frequency ventilation support when pneumatic diffusive convective "percussions" are inflated into the patient's airways with a certain frequency, thus developing the tidal volume (TV) required to maintain gas exchange [19]. The primary component of the PERCUSSIONAIRE device (Percussionaire Corporation, USA) is the Phasitron — a special frequency chopper developed based on the original idea of medical engineer Forrest M. Bird in 1980 in Idaho, USA. *Objective:* stimulation of mucociliary and cough clearance, increasing collateral ventilation, stimulation of pulmonary microcirculation, normalization of the ventilation/perfusion ratio, prevention of air trapping and collapses of small airways [20]. *Mechanism of action is «simple and ingenious»*. Firstly, the Phasitron is powered by compressed air (4–6 atmospheres) from a gas cylinder (mobile option) or an air compressor (high-pressure port, resuscitation console). Therefore, this device is universal, i.e., it is independent of an electrical power supply, which is crucially important when transporting the patient. Secondly, the Phasitron does not require spontaneous breathing of the patient, unlike most devices for noninvasive ventilatory support. Compressed gas moves the internal piston of the Phasitron back and forth, «cutting» airflow into «percussions» with a certain frequency. Percussion frequency can be adjusted in a wide range (from 100 to 1000 Hz). Percussions move progressively and create their own "tunnel/channel" (like, for example, a rotating bullet), which allows to deliver a portion of air/gas to the alveolar area. This delivery does not depend on the patient's participation in respiration. The "tunnel" does not allow a portion of moving air to exert pressure ("Pr") on the patient's airways, ensuring the creation of TV at zero «Pr» values (Fig. 2) [20].

Thirdly, the original solution to maintaining a constant TV required by the patient was the idea of an "open breathing circuit" that allows to get an additional portion of air from the outside, if necessary (required fraction of inspired oxygen, FiO_2, is maintained), or "expire" a portion of air (no resistance on expiration). In practice, this enables to avoid using oxygen blenders/mixers completely, enables to humidify air, dramatically reduces the consumption of "working gas", and allows combination with a nebulizer for timely delivery of the drug substance. Also, according to Newton's third law (action and reaction law), translational percussions reaching the alveolar zone cause reverse pneumatic shocks and air movement outside (named "Bird flows" after the inventor of this idea). This helps enhance the drainage of tracheobronchial secretion and sputum, activates regular contractions of the ciliary epithelium, which restores/normalizes mucociliary clearance (Fig. 3) [20].

The fourth unique property of the Phasitron is the biological "patient-device" feedback achieved via automatic "resistance/pressure" adjustment. The system, which is based on the law of energy conservation, automatically increases the flow rate when pressure falls and reduces it when pressure rises. This completely prevents barotrauma in areas with high resistance ("high narrowness"), making this device very safe even in newborns, when other methods of noninvasive ventilation support are almost impossible. In addition, this facilitates high "recruitment" of alveoli in gas exchange and stimulates the perfusion of previously quiet zones of lungs. Thus, the main mechanisms of action of IPPV therapy are associated with the following [21]:

- involvement of pulmonary structures in gas exchange, or "lung recruitment";
- mobilization and expectoration/coughing up of tracheobronchial secretion;
- increased diffusion capacity of lungs;
- improvement of bronchial blood flow and pulmonary microcirculation;
- restoration of air flow and elimination of «air trappings».

<u>*The procedure is preferably performed as follows*</u> [10]:

1. The patient in a sitting position performs relaxed breathing in the usual rhythm.
2. The patient breathes in and out at the usual rate through the mouthpiece of the Phasitron, avoiding unproductive cough at the beginning of expiration; the basic percussion frequency well tolerated by the patient should be adjusted using a controller; this stage should not be longer than 5 minutes.

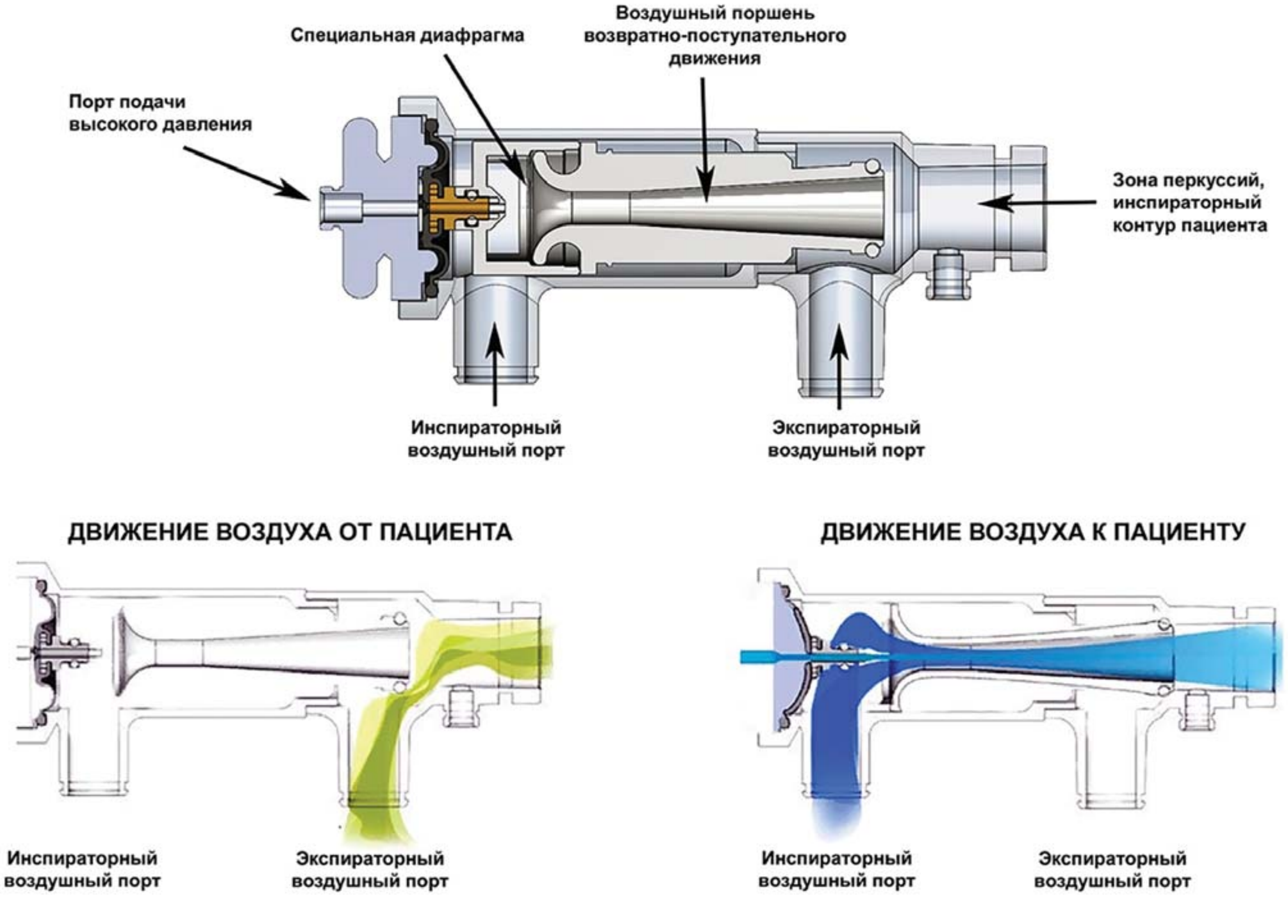

Figure 2. *Device diagram of the «Phasitron» block. Vertical section. The explanation in the text. (Source: Percussionaire Corp., Sandpoint, Idaho 83864 USA. [Electronic resource]. URL: https://percussionaire.com/products/phasitron. (date of the application: 22.12.2020))*

3. The patient continues breathing in/out through the mouthpiece of the Phasitron; the percussion frequency is doubled with the help of the controller; if a productive cough appears, coughing up is possible; this stage should not be longer than 15 minutes.
4. The patient continues breathing in/out through the mouthpiece of the Phasitron; the percussion frequency is lowered to the «basic» frequency with the help of the controller; if a productive cough appears, coughing up is possible; this stage should not be longer than 5 minutes.

The total duration of this procedure should not exceed 30 minutes; it can be repeated up to 4 times a day since premature fatigue of patient is possible.

3.2. Mechanical insufflation/exsufflation with oscillations

The idea of mechanical support of the patient's cough reflex is implemented in mechanical insufflation/exsufflation (MI-E) devices. An MI-E device is an air insufflator/exsufflator that allows to create a pressure drop in the patient's airways in a short time, which is consistent with the inspiratory/expiratory phase. This stimulates a cough reflex and enhances mucociliary clearance with expectoration. As a result, such devices were called «coughing machines» [22]. Objective: stimulation of mucociliary and cough clearance, respiratory muscle training. Mechanism of action: based on cough stimulation during a sharp drop in airway pressure. A 10 Hz oscillation is applied to the patient circuit for stabilizing the airway lumen to prevent barotrauma during insufflation (up to +60 mbar) and early expiratory collapses of small bronchi during exsufflation (up to –60 mbar) (Fig. 4). One of the most interesting MI-E devices is the Cough Assist E70 (Philips Respironics, USA) [23].

Absolute contraindications to MI-E [24]: 1) bullous pulmonary emphysema; 2) history of pneumothorax and barotrauma; 3) uncontrolled suffocation attack; 4) severe hypotension and/or pulmonary hemorrhage; 5) complete collapse of the upper RT (silent lung).

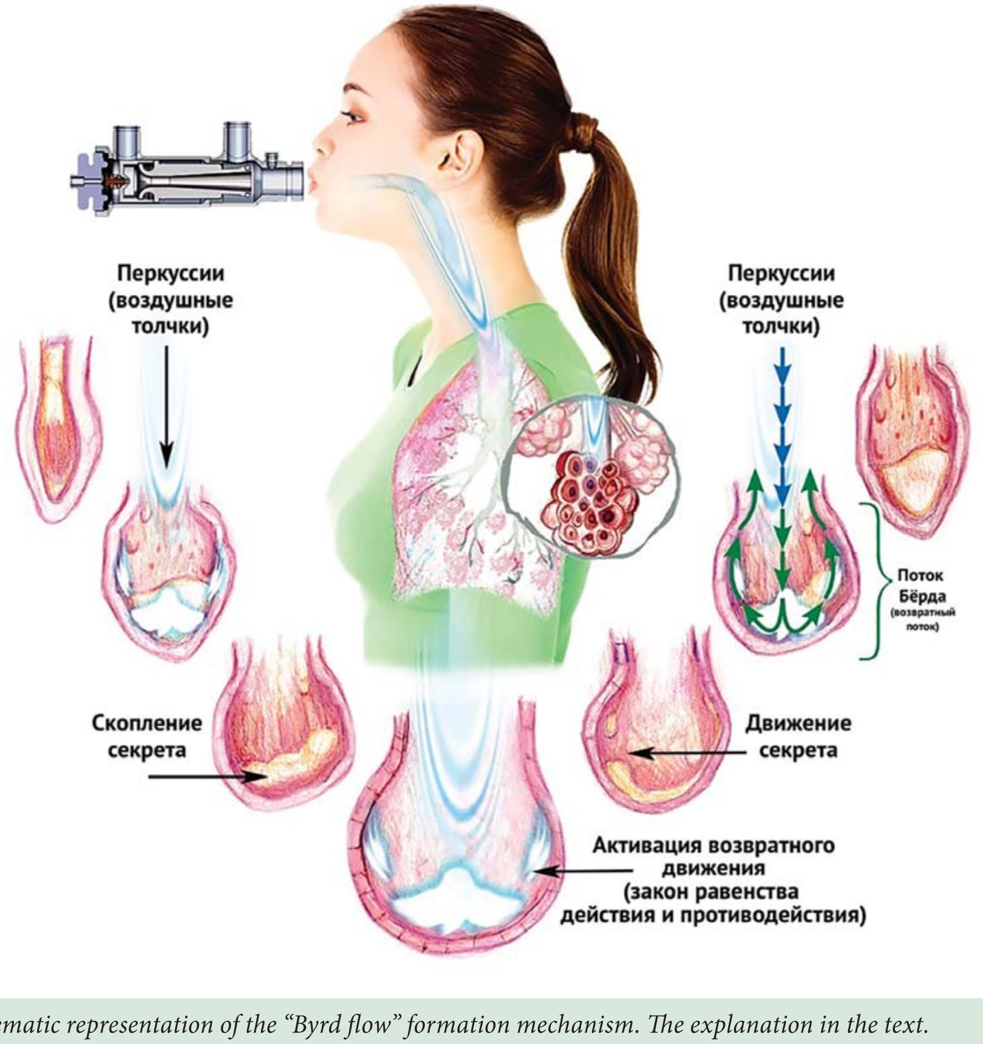

Figure 3. *Schematic representation of the "Byrd flow" formation mechanism. The explanation in the text. (Source: Percussionaire Corp., Sandpoint, Idaho 83864 USA [Electronic resource]. URL: https://percussionaire.com/products/travel-air. (date of the application: 22.12.2020))*

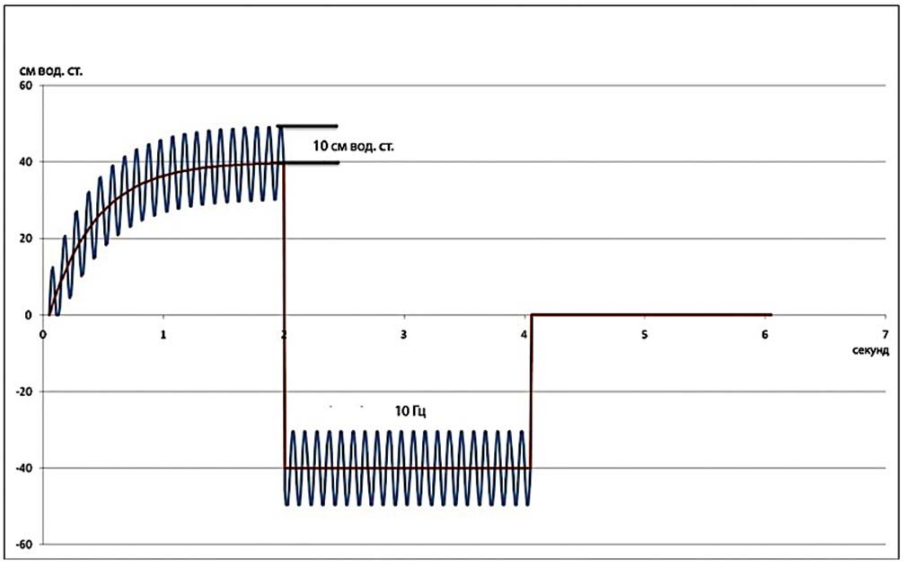

Figure 4. *Diagram of the insufflation/exufflation mechanism with oscillations. The blue line shows the pressure curve (+40 cm H_2O / -40 cm H_2O) at 10 Hz oscillations in the inhale/exhale phase lasting 2 seconds. (Adapted By: CoughAssist E70. Philips Respironics. [Electronic resource]. URL: https://philipsproductcontent.blob.core.windows.net/assets/20170908/b932adc03e96f6f21f2b8512458fa06f.pdf (date of the application: 22.12.2020))*

Patients in the following circumstances require particular attention and monitoring: 1) when carrying out the procedure after eating; 2) with gastroesophageal reflux; 3) with a sharp increase in RR; 4) with hemodynamic instability; 5) with severe bronchospasm; 6) with severe chest pain. The procedure is preferably performed as follows [10]:

1. The patient is in a sitting position and performs relaxed breathing in the usual rhythm.
2. The patient makes a 2–3 second inspiration through a mask (parameters should be preset in «automatic» mode, inspiration duration 0–5 seconds, with a 0.1 interval and oscillation frequency 10 Hz), avoiding unproductive cough at the beginning of inspiration.
3. The patient makes a 2–5 second expiration through a mask (parameters should be preset in «automatic» mode, expiration duration 0–5 seconds, with a 0.1 interval and oscillation frequency 10 Hz), avoiding unproductive cough at the beginning of expiration.
4. Repeat the inspiration/expiration cycle through a mask; a well-tolerated frequency of 1–20 Hz should be adjusted with the help of an oscillation controller; if a productive cough appears, coughing up is possible.

The total duration of this procedure should not exceed 30 minutes; it can be repeated up to 4 times a day since premature fatigue of patient is possible.

3.3. Long-term low-flow oxygen therapy

Long-term low-flow oxygen therapy (LTOT) is a method of restoring gas exchange function in cases of significant resting hypoxemia, defined as PaO_2 £ 55 mm Hg (7.3 kPa), or proven chronic hypoxemia PaO_2 56–59 mm Hg (7.4–8.0 kPa) in patients with pulmonary heart disease, polycythemia, pulmonary hypertension. The LTOT criterion in patients with physiological hemoglobin level is arterial blood oxygen saturation (SpO_2) less than 88% [6, 25]. Objective: elimination/minimization of respiratory failure (RF), stimulation of mucociliary clearance. Mechanism of action: based on the ability of oxygen with moderate concentration (21% < FiO_2 < 60%) and low flow (< 5.0 l/min) to stimulate metabolic processes in tissues, mucociliary clearance and to maintain physiological constancy of oxygen tension in arterial blood (PaO_2)). To perform LTOT at home, oxygen concentrators — portable medical devices that divide air (FiO_2 = 21%) into nitrogen (N_2) and oxygen (O_2) fractions — are used. With its maximum compliance for the patient and effective delivery of gas mixture, the nasal canula is regarded as the optimal device for performing LTOT at home. It should be noted that the actual value of FiO_2 depends on the geometry of the nasopharynx, oral breathing, minute ventilation, respiratory pattern (tidal volume and minute lung ventilation) [10].

The procedure is preferably performed as follows [25]:

- The duration of LTOT should exceed 15 hours/day; LTOT for 24 hours may yield additional benefits.
- LTOT is started at a flow of 1.0–1.5 l/min and is titrated stepwise (step of 0.5 l/min) until SpO_2 > 93% is reached.
- In patients who remain physically active, LTOT should be combined with additional oxygen therapy, especially during exercise.

- LTOT should be controlled every three months by analyzing arterial blood gas composition to assess the further effectiveness of the procedure.
- Control visits at the 6th and 12th month of LTOT should be carried out by a clinician with special training in respiratory medicine.

4. DRUG REHABILITATION THERAPY

A specific feature of drug rehabilitation therapy is its effect on the patient, depending on the patient's comorbidities. In the case of low comorbidity, the effectiveness of drug rehabilitation therapy is doubtful [6, 26, 27].

4.1. Bronchodilator therapy (combined bronchodilators)

Combined bronchodilator therapy should be performed in patients with proven airway obstruction of different severity. In patients with no obstructive disorders, such therapy is directly associated with side and undesirable effects from the cardiovascular system, especially in the case of drug overdose in individuals receiving it for the first time. If necessary, a rational combination of short-acting beta-2 agonists (SABA) and anticholinergics (SAAC) with their retard forms is possible. In post-COVID-19 patients with chronic obstructive pulmonary disease (COPD), the possibility of severe COPD exacerbation increases significantly. Such cases require a rational combination of long-acting beta-2 agonists (LABA) and long-acting anticholinergics (LAAC), which are the basic treatment for COPD with nebulized delivery of SABA + SAAC in high doses for 2–6 weeks. Post-COVID-19 patients with bronchial asthma (BA) may experience an increase in bronchial hyperreactivity and/or moderate exacerbation of BA. In such cases, ramping up treatment for BA with high doses of inhaled corticosteroids (ICS) and nebulized delivery of SABA + SAAC in high doses for 4–8 weeks is preferable [6, 26].

4.2. Mucolytic therapy

Most post-COVID-19 patients may develop impaired mucociliary clearance because novel coronavirus SARS-CoV-2 has a strong negative effect on bronchopulmonary segments (edema, inflammation, hypersecretion of tracheobronchial secretion, increased bronchial obstruction) [28], which makes long-term administration (> 1 month) of mucoactive agents relevant. Mucolytic therapy is most advisable in patients with chronic cough (> 8 weeks) and hard-to-remove sputum. The group with "peripheral action" (levodropropizine), which suppresses the release of neuropeptides and histamine, is usually identified among "anti-tussive medications". These agents have no negative effect on the central nervous system and mucociliary transport. In cases of a "debilitating" unproductive cough, non-codeine central-acting drugs (butamirate) that reduce the excitability of the cough center can be prescribed. However, detoxifying mucolytics (carbocysteine, N-acetylcysteine, erdosteine) and mucolytics that stimulate the motor and secretory function of the respiratory tract (ambroxol) are essential in that context.

4.3. Systemic corticosteroid therapy

The administration of systemic glucocorticosteroids (SGC) to patients after COVID-19 remains difficult to understand and debatable. Obviously, morphological changes in lungs of post-COVID-19 patients («ground-glass opacity» revealed by chest multispiral computed tomography (MSCT)) may persist for a long time (more than 90 days), which demonstrates the existence of a late slow phase of exudative changes; signs of «general inflammatory reaction» (weakness, asthenia, low-grade fever, loss of appetite) without evidence of bacterial infection may persist, raising the prospect of SGC therapy. At the same time, well-known side effects of such therapy (hyperglycemia, arterial hypertension, gastropathy, bacterial superinfection, osteoporosis) make a strong case against this treatment strategy [29]. However, post-COVID-19 patients with «ground-glass opacity» after day 90 of the disease are recommended to start low-dose SGC therapy with methylprednisolone (4–8 mg) for 1.5–3.0 months. Arguments for such treatment strategy are based on the extreme similarity of pulmonary MSCT findings in post-COVID-19 patients with radiological signs of «pulmonary vasculitis» that are effectively managed by SGC therapy. High-dose SGC therapy, monoclonal, anti-interleukin-6 (tocilizumab) therapy, including for the elimination of the «cytokine storm», is not relevant at the post-COVID-19 rehabilitation stage [6, 29].

4.4. Other drug rehabilitation therapy

Mild pulmonary arterial hypertension (PAH) (< 50 mm Hg) in post-COVID-19 patients requires no additional drug use and is resolved spontaneously by day 90 of the disease. However, if clinical symptoms of PAH are persistent and severe, therapeutic doses of diuretics, amlodipine, sildenafil should be prescribed. The administration of bosentan and prostanoids is justified only in cases of progressive PAH. The anti-inflammatory pleiotropic effect of statins on small vessels and bronchi and the additive effect of low doses of selective β-adrenergic blockers («overregulation» effect) are proven in post-COVID-19 patients with cardiovascular comorbidity. On the other hand, the management of arterial hypertension (AH) in such patients requires high doses of angiotensin-converting enzyme inhibitors (ACE inhibitors) due to their effect on angiotensin II (the most important component of inflammatory response in cases of COVID-19) [6].

Conclusion

Modern medicine has a broad range of drug and non-drug methods for the rehabilitation of post-COVID-19 patients. In addition, selecting proper rehabilitation methods and patient-specific rehabilitation programs with consideration of the individual clinical situation allows to avoid/prevent functional disorders and restore the quality of life in post-COVID-19 patients.

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