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Application of the Technique of Extracorporeal Membrane Oxygenation in a Patient with Respiratory Distress Syndrome Associated with Myasthenia Gravis

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RELEVANCE

Myasthenia gravis is an autoimmune neuromuscular disease characterized by pathologically rapid fatigue of striated muscles [1]. The main symptom of myasthenia gravis is the presence of pathological muscle weakness with involvement of the ocular, bulbar and skeletal muscles in the pathological process. The provoking factors for the development of myasthenia gravis can be infectious diseases, surgery, drugs [2, 3]. The main danger is represented by myasthenic and cholinergic crises, which are characterized by a severe course and high mortality; therefore, the problems of treating myasthenia gravis are still of high medical and social significance. The prevalence of myasthenia gravis is 17.5–20.3 per 100 thousand population, and the number of patients is increasing by 5–10% annually [4, 5]. In recent years, there has been a steady increase in morbidity with an increase in age over 50 years [6, 7]. Myasthenia gravis is a serious disease with a high mortality rate of up to 30–40% [3]. There are difficulties in the early differential diagnosis of muscle weakness in patients with respiratory failure between myasthenia gravis, myasthenic syndrome and critical illness polyneuropathy. These difficulties and insufficient awareness of patients and doctors of various specialties about myasthenia gravis can lead to the choice of the wrong treatment tactics and the development of myasthenic crisis, which is manifested by respiratory failure, requiring respiratory support. The progression of respiratory failure against the background of myasthenic crisis may require the use of extracorporeal membrane oxygenation (ECMO).

It is necessary to expand the differential diagnosis of muscle weakness in a patient during the period of resolution of respiratory failure, allowing to move away from compulsory respiratory support, termination of ECMO.

Keywords: extracorporeal membrane oxygenation; myasthenia gravis; myasthenic syndrome; autoimmune neuromuscular disease

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ABB – acid-base balance

ACT – active clotting time

ALV – artificial lung ventilation

ARDS – acute respiratory distress syndrome

BP – blood pressure

CAD – coronary artery disease

ECMO – extracorporeal membrane oxygenation

FBS – fibrobronchoscopy

HR – heart rate

MAP – mean airway pressure

PE – pulmonary embolism

RR – respiratory rate

RELEVANCE

Myasthenia gravis is an autoimmune neuromuscular disease characterized by pathologically rapid fatigability of striated muscles [1]. The main symptom of myasthenia gravis is the presence of pathological muscle weakness with involvement of the ocular, bulbar and skeletal muscles in the pathological process. The provoking factors for the development of myasthenia gravis can be infectious diseases, surgery and drugs [2, 3]. The main danger is presented by myasthenic and cholinergic crises, which are characterized by a severe course and high mortality; therefore, the problems of treating myasthenia gravis are still of high medical and social significance. The prevalence of myasthenia gravis is 17.5–20.3 per 100,000 population, and the number of patients is increasing by 5–10% annually [4, 5]. There has been a steady increase in morbidity with an increase in age over 50 years recently [6, 7]. Myasthenia gravis is a severe disease with a high mortality rate of up to 30–40% [3]. There are difficulties in the early differential diagnosis of muscle weakness in patients with respiratory failure between myasthenia gravis, myasthenic syndrome and critical illness polyneuropathy. These difficulties and insufficient awareness of patients and doctors of various specialties about myasthenia gravis can lead to the choice of the wrong treatment tactics and the development of myasthenic crisis, which is manifested by respiratory failure requiring respiratory support. The progression of respiratory failure in the course of myasthenic crisis may require the use of extracorporeal membrane oxygenation (ECMO).

It is necessary to expand the differential diagnosis of muscle weakness in a patient during the period of resolution of respiratory failure, which would allow to abandon compulsory respiratory support, terminate ECMO.

INTRODUCTION

Pneumonia is a wide group of infectious diseases of various etiology, pathogenesis and morphological characteristics, leading to impaired gas exchange function of the lungs, up to the development of acute respiratory distress syndrome (ARDS) [8]. Sometimes the course of pneumonia can be extremely severe, and the generally accepted methods of external respiration replacement, artificial ventilation of the lungs (ALV), are ineffective. In this case, the use of extracorporeal membrane oxygenation (ECMO) is the only way to save the patient [9]. One of the reasons for the development of pneumonia may be the presence of autoimmune neuromuscular diseases in the patient. In our clinical example, a case of progression of myasthenia gravis is described, against the background of which an infectious complication of the lungs developed.

In clinical observation, we demonstrate a rare combination of severe pneumonia with the development of ARDS, which required ECMO procedure in the presence of previously undetected myasthenia gravis in the patient. In the absence of timely diagnosis of neuromuscular disease, the duration of the membrane oxygenation procedure can be increased, thereby increasing the risk of complications (hemorrhagic, septic, thrombotic).

Aim of study: to describe the features of ECMO in the course of myasthenic crisis using the example of a clinical case.

MATERIAL AND METHODS

Observation of a clinical example using veno-venous ECMO with the Cardiohelp System (Maquet, Rastat, Germany).

Clinical observation

Patient U., 65 years old, female, was admitted on the 5th day from the onset of the disease to the department of anesthesiology and intensive care of the primary hospital with a diagnosis: "Community-acquired viral-bacterial bilateral pneumonia of a severe course. ARDS. Coronary artery disease: atherosclerotic cardiosclerosis. Hypertensive disease stage III, 3rd degree, risk of cardiovascular complications 4. Chronic heart failure Art. 2A. *NYHA* functional class III. Diabetes mellitus type 2, the target level of glycated hemoglobin is less than 7.5%. Obesity of the 3rd degree." From the anamnesis of the disease it is known that the patient had catarrhal phenomena, low-grade fever 9 days before the onset of the disease. It is also known that the patient previously did not have surgical interventions and anesthetic aids. No negative allergic anamnesis.

The patient was admitted in critical condition: severe respiratory failure (respiratory rate (RR) 42 per minute, oxygen saturation (SpO_2) 82%, cyanosis of the skin, inhibition of the level of consciousness to sopor according to the Glasgow coma scale – score 11 and hypotension (blood pressure (BP) 85/55 mm Hg, heart rate (HR) 136 beats/min), was transferred to mechanical ventilation, vasopressor support was started (norepinephrine at a dose of 0.28 μg/kg/min). An additional examination (chest x-ray) revealed a subtotal infiltrative lesion of the lung tissue, atelectasis of the lower lobes of the lungs, small bilateral hydrothorax.

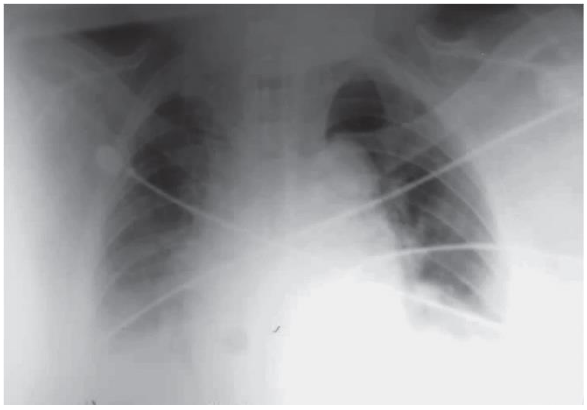

Fig. 1. Chest X-ray upon admission

Echocardiography: thickening of the walls of the aorta, the cusps of the aortic and mitral valves. The dimensions of the heart chamber were within normal limits. There were no violations of the general and local contractility of the left ventricle (LV). Velocity indicators of the valves were within normal limits. No

hemodynamically significant regurgitation was found. Violation of left ventricular (LV) diastolic function according to type 1. The pressure in the pulmonary artery was 32 mm Hg (the norm is 25-30 mm Hg).

During sanitary-diagnostic fibrobronchoscopy (FBS), significant inflammatory changes in the bronchi were revealed.

Despite the ongoing respiratory therapy with the recruitment maneuver and the use of prone-position, the patient's condition progressively deteriorated over time, the ventilation parameters were not within her protective framework. Pressure control ventilation (PCV) was performed, tidal volume 280 ml *(Vt),* respiratory rate 20 per minute (F), mean airway pressure 18 cm Aq (MAP), positive end-expiratory pressure 16 cm Aq (PEEP), the oxygen concentration of the inhaled mixture was 90% (FiO_2), while the acid-base state indicators corresponded to mixed acidosis: pH 7.26, partial pressure of oxygen in arterial blood (PaO_2) 56 mm Hg, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) 72 mm Hg ($PaCO_2$), true bicarbonate of arterial blood (HCO_3 - atc) 11 mmol/l, partial pressure of oxygen in arterial blood/oxygen concentration of the inhaled mixture (PaO_2/FiO_2) less than 62.

Given the course of the disease and the ineffectiveness of mechanical ventilation, the only way to resolve critical hypoxemia in this case was ECMO. The visiting team of the ECMO-Center of State Scientific Center - A.I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency, 5 days after admission to the clinic of primary hospitalization (on the 10th day from the onset of the disease), the IV ECMO was initiated with the parameters: 2850 rpm; oxygenated blood volume - 3.9 l/min *(V),* oxygen flow 5 l/min (*Flow* O_2), systemic anticoagulation with heparin 350 U/h under the control of active clotting time *(ACT)* 186 s, followed by transportation of the patient to the department of anesthesiology and resuscitation no. 2 of State Scientific Center - A.I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency for further treatment.

Against the background of antibiotic therapy and ECMO, the patient's condition improved, by the end of the first day of stay at State Scientific Center - A.I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency (1st day from the onset of ECMO, 11th day from the onset of the disease), it was possible to achieve normal blood gas parameters (pH 7.38, PaO_2 122 mm Hg, $PaCO_2$ 37 mm Hg, HCO_3 - *atc* 24 mmol/l, SpO_2 96%) and hemodynamic stabilization (BP 124/68 mm Hg, pulse rate 69 beats/min, norepinephrine 0.1. mg/kg/min). ECMO parameters: *RPM* 2688 rpm, *V* 3.5 l/min, *Flow* O_2 3 l/min, *AST* 180 sec. Mechanical ventilation was continued with safe parameters in *PCV* mode : *Vt* 440 ml, *F* 16/min, *PEEP* 12 cm aq, *MAP* 14 cm aq, FiO_2 30%, SpO_2 96–97%.

On the 2nd day from the onset of ECMO (12th day from the onset of the disease), due to the predicted long-term mechanical ventilation, a rotational puncture-dilated tracheostomy was performed with the Frova technique.

According to the conducted virology tests, the influenza virus was not detected, which, most likely, confirms the bacterial etiology of pneumonia.

On the 4th day from the onset of ECMO (14th day from the onset of the disease), there was a positive trend - resolution of gas exchange disturbances (pH 7.48, PaO_2 82 mm Hg, $PaCO_2$ 32 mm Hg, HCO_3 - *atc* 24 mmol/l, PaO_2/FiO_2 285), improvement of respiratory parameters in the patient (mechanical ventilation in *PCV* mode : *Vt* 520–550 ml, *F* 15 per min, *PEEP* 10 cm Aq, *MAP* 11–12 cm Aq, FiO_2 35%, SpO_2 96%), decreased blood oxygenation ECMO (1710 rpm, *V* 1.95 L/min, oxygen flow stopped, systemic anticoagulation with heparin 300 U/h, *ACT* 172 sec).

Despite the favourable X-ray picture of the lungs (Fig. 2), the patient did not have any attempts to inhale spontaneously. She also had impaired swallowing and lack of work of the chest respiratory muscles, tetraparesis.

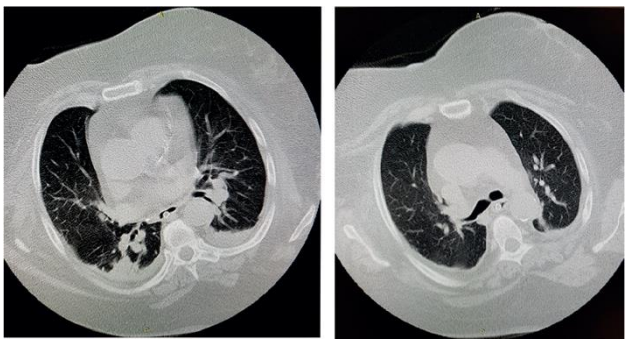

Fig. 2. Computed tomography of the chest organs before cessation of veno-venous extracorporeal membrane oxygenation

Taking into account the presence of a specific neurological clinical picture, the manifestation of an autoimmune neuromuscular disease with pneumonia was suspected. A decrement test was performed, according to which signs of impaired synaptic transmission in the cranial and skeletal muscles were revealed. Laboratory studies were carried out, according to which the patient was found to have antibodies to acetylcholine receptors, 0.68 nmmol/l (the norm is less than 0.42 nmmol/l).

Computed tomography of the chest was also performed: compared with the previous X-ray examination, the inflammatory process of the lung tissue on both sides was resolved, the phenomena of hypoventilation in the posterior parts of the right lung and hypoventilation decreased in the lower lobe of the left lung. In S2 on the right, a tough area of fibrosis with punctate calcifications still persisted. The roots of the lungs were structural. A tracheostomy tube was visualized in the tracheal lumen. The lumen of large bronchi was free. The intrathoracic lymph nodes were not enlarged. The heart was not noticeably enlarged. In the left pleural cavity there was a small amount of effusion. There were no data for masses in the mediastinum and thymus gland.

In order to exclude Guillain-Barré syndrome, a diagnostic lumbar puncture was also performed: protein in the cerebrospinal fluid was 0.1 g/l, protein-cell dissociation was not detected. Based on the data obtained, myasthenia gravis, myasthenic crisis were diagnosed. The first line of myasthenia gravis therapy was started - pulse therapy with glucocorticoids (intravenous methylprednisolone 1 mg/kg per day for the first 6 days, with the switch to the tablet form of methylprednisolone 0.5 mg/kg per day), as well as therapy with anticholinesterase drugs (pyridostigmine bromide 120 mg 4 times a day in tablet form, for a long time, with dosage adjustment according to the clinical picture) [10-12].

On the 5th day from the start of ECMO (15th day from the onset of the disease), against the background of the pulse therapy, the patient began to breathe independently, and hemodynamic stabilization with the cessation of vasopressor support was also noted. On the 6th day from the onset of ECMO (16th day from the onset of the disease), the patient began to attempt to swallow independently.

On the 7th day from the onset of ECMO (17th day from the onset of the disease), the ECMO procedure was discontinued (acid-base state of the blood: pH 7.5, PaO_2 81 mm Hg, $PaCO_2$ 33 mm Hg, HCO_3 - *atc* 234 mmol/L, PaO_2/FiO_2 242; ALV in *PSV* mode: *Vt* 515–560 ml, *F* 17–18 *bpm, PEEP* 10 cm Aq, *MAP* 9 cm Aq, FiO_2 35%, SpO_2 94%).

On the 18th day after the termination of ECMO (34th day from the onset of the disease), the patient was transferred to spontaneous breathing through a tracheostomy tube.

On the 20th day after the termination of ECMO (36th day from the onset of the disease), the patient was decannulated.

On the 37th day from the onset of the disease, the patient in a stable condition, with normal blood gas parameters, fully restored muscular strength of the pectoral muscles, without swallowing disorders, was transferred to the therapeutic department.

DISCUSSION

Taking into account that the patient had a specific neurological clinical picture (impaired swallowing, absence of spontaneous breathing, tetraparesis), the manifestation of an autoimmune neuromuscular disease with pneumonia was suspected. Differential diagnosis was carried out, followed by the diagnosis of the patient: "Myasthenia gravis, myasthenic crisis" (table).

Table

Differential diagnosis between the main causes of weakness of the respiratory muscles in the patient

Nosology	Guillain-Barré syndrome	Duchenne myodystrophy	Myasthenia gravis	Overdose of muscle relaxants
Etiology	Antibodies to gangliosides	Congenital defect in a gene that encodes a protein in muscle cells	Acetylcholine receptor antibodies	Overdose of muscle relaxants
Pathogenesis	Acute demyelinating inflammation of motor neurons	Gradual death of striated muscle fibers	Antibodies to own muscle tissue and thymus	Blocking acetylcholine receptors on the postsynaptic membrane
Diagnostic criteria	Deceleration of conduction along peripheral nerves, absence of *H*-reflex, absence or decrease in the amplitude of sensory potential, increased latency of *F*-waves. In 1 µl of cerebrospinal fluid, no more than 50 monocytes and/or 2 granulocytes	Analysis of dystrophin content in muscles, mutation analysis for the assessment of restriction fragment length polymorphism	Functional test to identify the syndrome of pathological muscle fatigue Positive decrement test Positive proserin test Blood test for antibodies to acetylcholine receptors, titin	Anamnestic data Positive proserin test Reversibility of action

Often, neuromuscular diseases affecting the respiratory muscles do not lead to respiratory failure, but only create favorable conditions for its development. Error or late diagnosis of myasthenia gravis are often noted, despite the simplicity of its clinical manifestations and the availability of diagnostic tests that confirm the diagnosis. The reason is that doctors do not have an idea of the pathognomonic symptoms of the manifestation of this disease, for which patients seek help at the beginning of the development of myasthenia gravis. In addition, diagnostic errors are sometimes associated with the similarity of myasthenia gravis in the early stages of its development with other diseases of the nervous system and muscles.

Methods for diagnosing myasthenia gravis are tests for autoantibodies to acetylcholine receptors and decrement test. Antibodies to the acetylcholine receptor are observed in 80–90% of patients with generalized myasthenia gravis, 80–90% of patients with paraneoplastic (thymoma-associated) myasthenia gravis, 50% of patients with ocular myasthenia gravis. The detection of a high content of antibodies to the acetylcholine receptor is a diagnostic sign for the diagnosis of myasthenia gravis, but a negative result does not exclude the disease, since its seronegative forms are often noted [13]. Monitoring titers in a particular patient may reflect the dynamics of the clinical course of the disease [14]. The decrement test is an electrophysiological test that evaluates the ability of a neuromuscular synapse to transmit excitation. The method is based on the phenomenon of a gradual decrease in the amplitude of muscle contraction, that is, a decrease in its decrement in response to cyclic stimulation [15].

The causes of myasthenia gravis decompensation can be infections, intoxication (due to infection). Any changes in hormonal levels and the use of drugs, including antibacterial drugs used for pneumonia, can also be a trigger mechanism for a crisis. With myasthenia gravis, disability often occurs, the quality of life is significantly reduced. The main danger is myasthenic and cholinergic crises, which are characterized by a severe course and high mortality. The causes of death are both myasthenia gravis itself and intercurrent diseases with equal frequency, in particular pneumonia [16]. Crises of myasthenia gravis can be mild, ceasing with a single injection of an anticholinesterase drug, and severe, requiring a wide range of resuscitation procedures and manipulations. The development of myasthenic crisis indicates a prognostically unfavorable course and is characterized by intense progression and generalization of the myasthenic process with impaired function of vital organs. And with damage to the muscles of the larynx, pharynx and epiglottis, breathing disorders of the pseudobulbar type often develop, which are manifested by the retraction of the tongue, epiglottis and obstruction of the upper respiratory tract with pharyngeal-tracheal secretions, which leads to the development of aspiration pneumonia.

ECMO procedure is increasingly performed as life-saving treatment for severe violations of external respiration. The duration of the procedure may vary and depends on the severity of the course of the pneumonia. According to the literature, the average duration of IV-ECMO in adults with acute respiratory failure is 10.5–13.5 days [17]. The severity of the course of pneumonia in some cases requires longer IV-ECMO procedure, and more information about prolonged ECMO has recently appeared in the medical literature. In 974 cases of extended ECMO procedure, the average age of patients is 40 (18–83) years, and the duration of ECMO in such cases is on average 25 days (14–208). The most common type of ECMO was veno-venous (79.5%), veno-arterial - much less frequently (9.9%). The reasons for the termination of ECMO included: restoration of lung gas exchange (54%), organ failure (23.7%), family request (6.7%), hemorrhagic complications (2.7%) and conditions incompatible with life (5.6%). ECMO for the treatment of severe respiratory diseases in adult patients is associated with an overall survival of 50–70% with a median ECMO procedure duration of up to 10 days [18]. The malicious course of pneumonia in some cases requires longer IV-ECMO, and recently more information has appeared in the medical literature about long-term (more than 14 days) ECMO [19].

The ECMO procedure is associated with the risk of developing many potentially fatal complications: massive bleeding, limb ischemia, subacute thrombosis, neurological complications (spontaneous intracranial hemorrhage, ischemic stroke, convulsive syndrome) [20, 21]. With the prolongation of the ECMO procedure, the risks of developing complications only become higher. Thus, the therapy and the tactics of patient management should be aimed at the shortest possible time for the procedure. However, the severe course of the underlying disease, complicated by antibiotic resistance of the causative agents of pneumonia and the development of fibro-destructive changes in the lung tissue, does not always allow terminating the ECMO procedure. The presence of neuromuscular conditions, including critical illness polyneuromyopathy, Guillain-Barré syndrome and myasthenia gravis, significantly complicates the termination of both ECMO and mechanical ventilation [22, 23]. These diseases need to be diagnosed and differentiated among themselves for the timely initiation of the necessary specific therapy. Adequate

therapy of concomitant neuromuscular pathologies significantly reduces the time required for the ECMO procedure. In this clinical example, most specialists initially regarded the weakness of the respiratory muscles as a manifestation of Pickwick's syndrome, polyneuropathy of critical conditions and fatigue of the respiratory muscles against the background of prolonged mechanical ventilation, but timely myography made it possible to avoid prolongation of the ECMO procedure, and, accordingly, associated complications and possible death.

CONCLUSION

It is worth remembering that various neuromuscular diseases can be one of the reasons for the difficult termination of mechanical ventilation and extracorporeal membrane oxygenation. If severe muscle weakness is detected in patients, it is advisable to conduct myography to diagnose myasthenia gravis and Guillain-Barré syndrome, requiring specific therapy, without which the restoration of adequate spontaneous breathing takes a long time.

Further accumulation of experience in the management of patients with previously undetected neuromuscular diseases with severe impaired respiratory function, requiring extracorporeal membrane oxygenation, will help develop unified management algorithms for this group of patients, which will contribute to timely diagnosis, treatment and improvement of outcomes.

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