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Case report

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Adrenal Dysfunction in Severe Community-Acquired Pneumonia Requiring Veno-Venous Extracorporeal Membrane Oxygenation

***N.E. Altshuler*[1] ✉, *N.M. Kruglyakov*[1], *G.I. Bagzhanov*[1], *A.A. Dokukin*[2], *K.K. Gubarev*[1], *M.B. Kutsyi*[2], *K.A. Popugaev*[1, 3]**

Department of Anesthesiology, Reanimatology and Intensive Care
[1] A.I. Burnasyan Federal Medical Biophysical Center
23, Marshala Novikova Str., Moscow 123098, Russian Federation
[2] European Medical Center
3, Shepkina Str., Moscow 129090, Russian Federation
[3] N.V. Sklifosovsky Research Institute for Emergency Medicine
3, Bolshaya Sukharevskaya Sq., Moscow 129090, Russian Federation

✉ **Contacts:** Natavan E. Altshuler, Candidate of Medical Sciences, Assistant of the Department of Anesthesiology, Reanimatology and Intensive Care, Medical and Biological University of Innovation and Continuing Education, A.I. Burnasyan Federal Medical Biophysical Center. Email: natavan.altschuler@gmail.com

ABSTRACT The article presents a clinical case of adrenal dysfunction in a patient with severe community-acquired pneumonia requiring extracorporeal membrane oxygenation. We discuss the lack of diagnostic criteria for adrenal dysfunction in critical conditions; the tactics of hydrocortisone treatment: initiation of use, its duration, dose titration and withdrawal conditions.

Keywords: critical illness, hydrocortisone, cortisol, extracorporeal membrane oxygenation, adrenal glands, adrenocorticotropic hormone

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Affiliations

Natavan E. Altshuler	Candidate of Medical Sciences, Assistant of the Department of Anesthesiology, Reanimatology and Intensive Care, Medical and Biological University of Innovation and Continuing Education, A.I. Burnasyan Federal Medical Biophysical Center; https://orcid.org/0000-0001-5646-0055, natavan.altschuler@gmail.com; 30%, concept and design of the study; collection, analysis and interpretation of data; analysis of literature on the research topic; scientific editing; approval of the final text of the article; significant contribution to the research
Nikolay M. Kruglyakov	Anesthesiologist-Resuscitator, Head of the Department of Resuscitation and Intensive Care, A.I. Burnasyan Federal Medical Biophysical Center of the Federal Medical Biological Agency; https://orcid.org/0000-0001-5011-6288, nik160@mail.ru; 20%, collection, analysis and interpretation of data, scientific and technical editing
German I. Bagzhanov	Assistant of the Department of Anesthesiology, Reanimatology and Intensive Care, Medical and Biological University of Innovation and Continuing Education, A.I. Burnasyan Federal Medical Biophysical Center; https://orcid.org/0000-0003-3363-5195, bag_g1992@gmail.com; 16%, collection, analysis and interpretation of data, scientific and technical editing
Aleksey A. Dokukin	Anesthesiologist-Resuscitator, European Medical Center; https://orcid.org/0000-0003-1837-3588, gneezdo777@mail.ru; 14%, collection, analysis and interpretation of data, scientific and technical editing, approval of the final text of the article
Konstantin K. Gubarev	Candidate of Medical Sciences, Head of the ECMO Center; Head of the Surgical Department for Coordination of Organ and (or) Human Tissue Donation, A.I. Burnasyan Federal Medical Biophysical Center; https://orcid.org/0000-0001-9006-163X, kkgubarev@gmail.com; 10%, collection, analysis and interpretation of data, scientific and technical editing
Mikhail B. Kutsyi	Candidate of Medical Sciences, Head of the Surgical Center, European Medical Center; https://orcid.org/0000-0003-0096-905X, mkutsyy@gmail.com; 6%, scientific and technical editing, approval of the final text of the article

Konstantin A. Popugaev Doctor of Medical Sciences, Professor of the Russian Academy of Sciences, Deputy Director-Head of the Regional Vascular Center of the N.V. Sklifosovsky Research Institute for Emergency Medicine; Head of the Department of Anesthesiology, Reanimatology and Intensive Care, Medical and Biological University of Innovation and Continuing Education, A.I. Burnasyan Federal Medical Biophysical Center;
https://orcid.org 0000-0003-1945-323X, stan.popugaev@yahoo.com;
4%, concept and design of the study, scientific and technical editing, approval of the final text of the article

ACTH – adrenocorticotropic hormone
CI – critical illness
CIAI – critical illness-induced adrenal insufficiency
ECMO – extracorporeal membrane oxygenation
HPA – hypothalamic-pituitary-adrenal axis
IV – intravenously
MV – mechanical ventilation of the lungs
RDS – respiratory distress syndrome
RR – respiratory rate
VV ECMO – veno-venous extracorporeal membrane oxygenation

Hemodynamic instability is a common finding during veno-venous extracorporeal membrane oxygenation (VV ECMO). Often the causes of arterial hypotension that occurs in patients with viral pneumonia during VV ECMO are decreased cardiac output, hypovolemia and sepsis. At the same time, none of the reasons are identified in most cases. Meanwhile, adrenal dysfunction is one of the possible causes of cardiovascular dysfunction. However, there are no studies that would study the incidence, causes, pathogenesis and clinical picture of adrenal dysfunction in patients undergoing VV ECMO for severe viral bilateral pneumonia. In this regard, at least until additional studies are conducted, the possibility of adrenal dysfunction should always be kept in mind if the patient population under study is hemodynamically unstable [1].

Patient K., 32 years old, was admitted to the primary hospitalization clinic with a diagnosis of community-acquired bilateral pneumonia on the 10th day of illness due to fever up to 39°C, increasing shortness of breath, and an x-ray picture of bilateral pneumonia. On admission, the level of consciousness corresponded to stuporous state; the Glasgow Coma Scale score was 13. On examination, breathing – spontaneous, respiratory rate (RR) – 45 breaths per minute, oxygen saturation in arterial blood – 65% with humidified oxygen insufflation at a rate of 10 l/min. Laboratory data: acid-base status of arterial blood: pH 7.43; partial pressure of carbon dioxide (pCO2) – 30.7 mmHg; partial pressure of oxygen (pO2) – 44.9 mmHg; hemoglobin - 118 g/l; blood level: potassium - 3.3 mmol/l; sodium - 142 mmol/l; lactate - 2.2 mmol/l; Base - 3.2 mmol/l; HCO3 - 22.0 mmol/l. Due to respiratory failure (respiratory index of less than 90%, pO2 of less than 60 mmHg, respiratory rate of more than 35 breaths per minute), the patient was transferred to mechanical ventilation (MV). Hemodynamics after transfer to MV were unstable and maintained by the administration of norepinephrine of 0.05–0.1 mcg/kg/min. Blood pressure - 127/75 mmHg. Virological test of the mucous membrane of the oropharynx - the causative agent of the H1N1 influenza virus. On the 6th day (16th day from the onset of the disease), taking into account the progression of respiratory failure, severe hypoxemia with increased oxygen fraction (FiO2) in the inhaled gas mixture up to 100%, and positive end-expiratory pressure up to12 cmH2O, a decision was made to initiate VV ECMO with subsequent (on the same day) transfer of the patient to the ECMO Center (Russian State Research Center – Burnasyan Federal Medical Biophysical Center of the Federal Medical Biological Agency).

At the time of admission to the ECMO Center, the patient's condition was extremely severe, consciousness was depressed by medication (propofol), the condition corresponded to 18 points on the Acute Physiology and Chronic Health Evaluation (APACHE II) scale, and 9 points on the Sequential Organ Failure Assessment (SOFA) scale. Ventilation was performed through an endotracheal tube in the BiLevel mode with the following parameters: respiratory rate – 12 breaths per minute, tidal volume – 380–440 ml, positive end-expiratory

pressure – 12 cmH2O, FiO2 – 50%, arterial blood oxygen saturation – 98–100 %. VV ECMO parameters: volume - 3.7 l/min, revolutions - 2460 ml/min, FiO2 - 3-4 l/min. By the time of admission, the patient's hemodynamics were unstable, supported by norepinephrine - 0.25 mcg/kg/min, blood pressure - 109/44 mmHg, heart rate 90 beats/min. A nasogastric tube was installed, the nature of the fluid flowing out showed traces of stagnant gastric contents; upon auscultation of the intestines, peristalsis was sluggish. Urination through the urethral catheter, in the urinal upon admission - 50 ml of concentrated urine. According to laboratory data: in the blood, the content of leukocytes is 11.1 × 109 / l, neutrophils - 8.9 × 109 / l, platelets - 143 × 109 / l, hemoglobin - 98 g / l, hematocrit - 28.3%; level of C-reactive protein - 149.9 mg/l, creatinine - 63.5 μmol/l, potassium - 3.9 mmol/l, sodium - 148 mmol/l, glucose - 9.9 mmol/l, procalcitonin - less than 0.5 ng/ml. Computed tomography of the chest, abdominal and pelvic organs showed a picture of bilateral polysegmental pneumonia with subtotal damage to the left lung (Fig. 1).

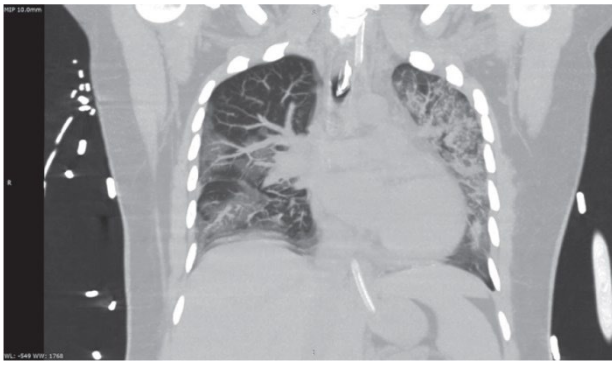

Fig. 1. Computed tomography of the chest on the day of admission to the Extracorporeal Membrane Oxygenation Center

Thus, the severity of the patient's condition at the time of admission was due to viral bilateral polysegmental pneumonia with the development of respiratory distress syndrome (RDS) and respiratory failure of the third degree, initially of viral origin, which required the connection of VV ECMO; as well as vascular failure. Diagnosis of adrenal dysfunction was based primarily on the need for norepinephrine of at least 0.25 mcg/kg/min.

When assessing the hypothalamic-pituitary-adrenal axis, the level of cortisol and adrenocorticotropic hormone (ACTH) in the blood plasma before the start of hydrocortisone administration was 406 mmol/l and 13 ng/dl on D0; 176 mmol/l on D1; and 129 mmol/l on D3; and on the day of weaning from VV ECMO - 252 mmol/l; while the level of ACTH in the blood plasma was 13 ng/dl on D0; 12 ng/dl on D1; 13.9 ng/dl on D3, 14.3 ng/ml on D5; and on the day of weaning from VV ECMO – 16.8 ng/dl. Plasma sodium levels since admission ranged from 139 to 149 mmol/L.

Due to vascular insufficiency and the need for norepinephrine of at least 0.25 mcg/kg/min on the day of transfer to ECMO (D0), hydrocortisone was added to therapy at an initial dose of 300 mg (100 mg

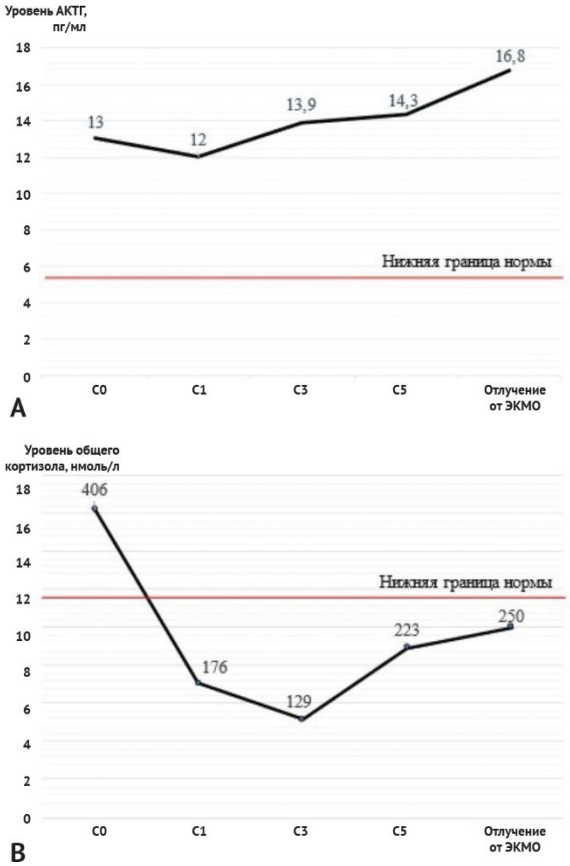

Fig. 2. Dynamics of the level of adrenocorticotropic hormone (ACTH) and total cortisol in the blood plasma during veno-venous extracorporeal membrane oxygenation (VV ECMO). Reference values: ACTH — 4.7–48.8 pg/ml, total cortisol in the development of critical conditions — above 275 nmol/l [2]

intravenous (IV) bolus, then 50 mg every 6 hours), on the 1st day and thereafter hydrocortisone was administered at a dose of 50 mg, IV bolus, 4 times a day. Against the background of intravenous administration of hydrocortisone at a dose of 200 mg per day, the need for norepinephrine during the 5th day of observation decreased to 0.05 mcg/kg/min, and on the day of weaning from VV ECMO (day 6) it was 0.05 –0.03 mcg/kg/min. Given the continued need for a small dose of norepinephrine, the dose of hydrocortisone was not reduced. On day 2 after weaning from VV ECMO, hemodynamics stabilized and norepinephrine administration was discontinued. From the 3rd day after weaning from VV ECMO (8th day from the moment of admission to the ECMO Center), a reduction in the dose of hydrocortisone was started by 25–50 mg per day, depending on the target blood pressure values. On the 7th day after weaning from VV ECMO, hydrocortisone was discontinued due to stabilization of blood pressure.

The level of consciousness from the first day of treatment in the ECMO Center was clear, the patient was oriented in her own personality and location. Sedation during the observation period was carried out with QUEtiapine and pregabalin. The duration of VV ECMO was 6 days. On the 5th day, antibacterial therapy was added to the patient treatment. During this period, when assessing the severity of the condition by the 5th day (D5), the SOFA score decreased to 7 points, and on the day of weaning from VV ECMO (D6) - to 6 points. The level of C-reactive protein on D0 was 83 mg/l, on D1–149 mg/l, on D2 –79 mg/l, on D3–131 mg/l, on D4–223 mg/l, on D5–143 mg/l, and on the day of weaning from VV ECMO – 114 mg/l . The content of leukocytes in the blood on D0 was 11.1×10^9/l, on D1–12.9×10^9/l, on D2–14×10^9/l, on D3–15×10^9/l, on D4–13×10^9/l, on D5–12.3×10^9/l, and on the day of weaning from IV ECMO –– 10.9×10^9/l.

After weaning the patient from VV ECMO, rehabilitation measures were started in the intensive care unit (ICU). On the 9th day from the moment of admission to the ECMO Center, the patient was transferred to spontaneous breathing with oxygen insufflation in a volume of 8 l/min. On the 12th day from the moment of admission to the ECMO Center, the patient was transferred to the pulmonology department with subsequent discharge from the Burnasyan Federal Medical Biophysical Center. At the time of transfer, the patient's condition was of moderate severity - she was in clear consciousness, spontaneously breathing with insufflation of humidified oxygen in a volume of 6 l/min.

It should be noted that H1N1-associated RDS can be a rapidly progressive disease. The features of the tropism of the virus to lung tissue and the speed of its replication allow it to develop rapid and almost total damage to the lungs. In addition, pronounced overproduction of inflammatory cytokines with the development of systemic endothelial dysfunction and microcirculation crisis allows us to characterize systemic H1N1 damage as viral sepsis [3]. The clinical course of H1N1-associated RDS differs significantly from RDS due to other causes, namely, it demonstrates a prolonged recovery of gas exchange in the lungs, which entails a frequent need for VV ECMO and a long stay in the ICU [4]. The combination of primary (viral) and secondary (inflammatory) lung damage not only ensures long-lasting disturbances in gas exchange and pulmonary perfusion, but also makes it easy for opportunistic bacterial flora to join the pathological process. Therefore, at the stage of advanced H1N1-associated RDS, most often we are talking about the course of combined viral-bacterial sepsis with multiple organ failure, one of the components of which is endocrinopathy of critical illness (CI).

Critical illness-induced adrenal insufficiency (CIAI) is based on dysregulation in the hypothalamic-pituitary-adrenal-target tissue axis at any level, which leads to decreased adrenal cortisol production and/or tissue resistance to glucocorticoids [5]. CIAI is characterized by dysregulation of systemic inflammation caused by inadequate intracellular glucocorticoid-mediated anti-inflammatory activity in CI patients. Dynamic changes in plasma concentrations of ACTH and total cortisol during CI development form a three-phase model (acute, subacute and chronic phases). The acute phase is most often characterized by an increase in the level of ACTH in the blood plasma

and, as a consequence, an increase in the level of cortisol in it. The subacute phase is characterized by a steady increase in the level of total and free cortisol in the blood plasma with a low level of ACTH in it. The chronic phase is characterized by the level of ACTH and cortisol in the blood plasma not higher than the reference values [6]. Within the three-phase model of CI (acute, subacute and chronic phases), the patient's condition requiring connection to ECMO can be considered as a subacute/chronic phase. This conclusion in our case is based on the following: initiation of connection to ECMO (16 days after the onset of the disease) and a decrease in cortisol levels over the entire period of ECMO. The recommended diagnostic criteria for CIAI are the determination of the concentration of total cortisol in the blood plasma or a stimulation test with synthetic ACTH [2]. The diagnosis of CIAI is established when a random determination of the total cortisol level in the blood plasma is less than 10 μg/dL (276 nmol/L) or when the delta of total cortisol is less than 9 μg/dL (249 nmol/L) from its initial level after intravenous administration of synthetic ACTH. At the same time, there is no certainty regarding the diagnostic criteria for CIAI: conducting the assessment of total blood cortisol or the test with synthetic ACTH. The reason for this is the insufficient number of studies, since one open single-center randomized study and a small number of cohort studies have been published [2].

Clinicians do not apply these diagnostic criteria in everyday practice, since interpreting the results of cortisol and ACTH evaluation, and conducting diagnostic tests does not provide an objective picture of the presence/absence of CIAI. When treating CI, immediate decision-making is required, and waiting for the results precludes the advisability of those diagnostic tests. Moreover, the Surviving Sepsis Campaign guidelines suggest that the synthetic ACTH stimulation test should not be used in patients with septic shock for treatment with hydrocortisone [3]. Despite this, the test with synthetic ACTH is considered superior to hemodynamic response to hydrocortisone for the diagnosis of CIAI [2].

The informative value of the diagnostic test with synthetic ACTH in assessing the content of total cortisol depends on the level of cortisol-binding protein and, to a lesser extent, on the level of albumin in the blood plasma [7, 8]. During CI, especially in sepsis, the level of corticosteroid binding globulin drops by 50%, resulting in an increase in the proportion of free cortisol [9]. In this case, the results of this diagnostic test to identify CIAI are not informative. Assessing free cortisol levels in ICU settings is difficult because it is not a routine method. The ability of the adrenal glands to respond to the administration of high doses of synthetic ACTH in the form of increased cortisol levels does not determine the validity of the hypothalamic-pituitary-adrenal (HPA) axis, since there is no information about the response of the HPA axis to stimuli such as hypotension and hypoglycemia. Conducting a test with a high dose of synthetic ACTH, apparently, is not a natural condition for the body, especially with the development of septic shock [10, 11].

Thus, on the one hand, there are no diagnostic standards for CIAI, but, on the other hand, the administration of hydrocortisone for the purpose of assessing the hemodynamic response is not recommended. Other diagnostic options were rejected due to “the inappropriateness of their implementation in intensive care conditions.” Carrying out stimulation tests does not reflect the presence of secondary and (or) tertiary adrenal insufficiency, affecting only the primary one, which limits the performance of those tests. To date, no data on the development of adrenal dysfunction when using ECMO in adults has been identified in the available literature.

Given the advisory nature of the diagnosis of CIAI, when prescribing hydrocortisone, we were based on the increasing need for norepinephrine and the need for it at a dose equal to or greater than 0.25 mcg/kg/min on the day of ECMO connection. At the same time, the analysis of the content of cortisol and ACTH in the blood plasma on the first day (D1) showed a decrease in the level of cortisol below the recommended values during CI against the background of a stable level of ACTH, without its tendency to increase. On the next days of observation, before weaning from ECMO, the level of

cortisol in the blood plasma remained below acceptable values, which confirmed adrenal dysfunction. During the administration of hydrocortisone, the daily dose of norepinephrine decreased, as well as the level of C-reactive protein and leukocytes, which increased until the 4th day; starting from D5, positive dynamics were observed in the form of a decrease in the severity of inflammatory markers. In addition, restoration of lung function was noted in the form of improved compliance and blood gas composition against the background of increased tidal volume, which made it possible to reduce the performance of the ECMO device with its subsequent shutdown. At the same time, a positive response in the form of a reduction in the dose of norepinephrine reflected the effectiveness of the use of hydrocortisone, which is confirmed by previous studies.

Therefore, patients with a long history of disease leading to the development of CI and the need for ECMO, with unstable hemodynamics and requiring the use of vasopressors should be considered as having adrenal dysfunction, and treated with hydrocortisone replacement therapy, without focusing on the levels of ACTH and cortisol in the blood plasma.

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