Review

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Adrenal Dysfunction Caused by a Critical Condition During Extracorporeal Membrane Oxygenation

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ABSTRACT Currently, the assessment of adrenal dysfunction in critically ill patients and ways to correct adrenal dysfunction with hormone replacement therapy are extremely difficult. The results of the Cochrane meta-analysis "Corticosteroids for treating sepsis" showed that survival was higher among patients with respiratory distress syndrome and septic shock who received glucocorticoids (mainly hydrocortisone) for a long course and at low doses. These results are in very good agreement with the concept of critical illness-related corticosteroid insufficiency (CIRCI) development in the subacute and chronic stages of a critical condition and the need to prescribe glucocorticoid replacement therapy in this situation. International guidelines for the treatment of sepsis and septic shock for 2016 suggest avoiding the use of hydrocortisone in patients who developed sepsis. Only the development of septic shock, and the persisting instability of hemodynamics against the background of achieving normovolemia and high doses of vasopressors, are the indication for the use of hydrocortisone 200 mg intravenously. In 2021, revised guidelines approved the administration of hydrocortisone to patients in septic shock without waiting for an adequate fluid loading to be achieved. In contrast to these recommendations, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, in their recommendations for 2017, suggest for adrenal dysfunction caused by a critical condition in patients with severe community-acquired pneumonia and circulatory arrest the use of hydrocortisone in the early stages, before the development of multiple organ failure. The existing guidelines do not consider the use of hydrocortisone in critical conditions during extracorporeal membrane oxygenation (ECMO). The timing of hydrocortisone administration to critically ill patients requiring ECMO, and the duration of this therapy are currently a topical issue for intensive care specialists. To ensure the completeness of the list of references for compiling a systematic review in the databases MEDLINE, PubMed, MeSH, eLibrary.EN a search was performed for matches, by keywords, and phrases, the roots of keywords, taking into account possible word forms, by the first two hundred relevant links, in case there were so many links. The exclusion criterion was "the use of synthetic glucocorticoids".

Keywords: hydrocortisone, adrenal insufficiency, adrenocorticotropic hormone, cortisol, septic shock, pneumonia, extracorporeal membrane oxygenation, ECMO, critical illness-related corticosteroid insufficiency, CIRCI

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ACTH – adrenocorticotropic hormone
GABA receptors – gamma-aminobutyric acid receptors
HPA – hypothalamus-pituitary-adrenal axis
CI – critical illness
CIRCI – critical illness-related corticosteroid insufficiency
ICU – intensive care unit
MOF – multiple organ failure
SIRS – systemic inflammatory response syndrome
ECMO – Extracorporeal Membrane Oxygenation

INTRODUCTION

The purpose of this review is to analyze the current periodical literature on the problem of critical illness-related corticosteroid insufficiency (CIRCI) and the outcomes of hydrocortisone therapy in critical illness (CI). The possibility of CIRCI development during extracorporeal membrane oxygenation (ECMO) is also theoretically considered.

Since CIRCI development is not a linear process, the review pays great attention to CI phases. To date, ECMO in CI has not been practically studied from the standpoint of CIRCI formation, and the authors of the review analyze the possibility of extrapolating data obtained in other CI cases.

The concept of CIRCI was first approved in 2008 by members of the Society for Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Adrenal dysfunction caused by CIRCI is based on dysregulation at any level in the hypothalamus-hypophysis-adrenal glands-tissue-target system, which leads to a decrease in adrenal cortisol production and (or) tissue resistance to glucocorticoids [1].

CIRCI is characterized by dysregulation of systemic inflammation due to inadequate intracellular glucocorticoid-mediated anti-inflammatory activity in CI patients. CIRCI is associated with increased levels of inflammatory markers, hypercoagulability, length of stay in the intensive care unit (ICU), and mortality [1, 2].

In 2017, recommendations for CIRCI diagnosis and treatment were revised. The revision was based on two emerging needs: recognition of the importance of a scientifically based approach to patient treatment in order to achieve a better result and patient safety; the widespread use of corticosteroids in CI patients highlights the need for a generally accepted, reliable and understandable way to assess CIRCI clinical signs [2].

ECMO is a temporary method of life support in CI, primarily associated with the development of severe respiratory and (or) heart failure. ECMO is not a therapeutic method to the full extent, but only an organ replacement measure that gives time to maintain adequate blood circulation, oxygenation of organs and tissues, and conduct pathogenetically substantiated therapy aimed at restoring a damaged organ or system [3]. The use of ECMO in the ICU conditions makes it possible to reduce the risk of adverse outcomes in CI. At the same time, the aggressiveness of this type of treatment carries the risk of complications [4]. Unfortunately, to date, there have been no studies on the assessment of CIRCI in adult patients during ECMO.

ADRENAL DYSFUNCTION CAUSED BY CRITICAL ILLNESS

Critical illness is a complex of pathophysiological changes in the body that require replacement of the functions of vital organs and systems in order to prevent imminent death [5].

Non-specific CIRCI symptoms include nausea, vomiting, fluid-resistant and catecholamine-resistant hypotension, hyponatremia, hyperkalemia, hypoglycemia, eosinophilia, lymphocytosis, and fever. Neurological disorders can manifest as delirium and coma [6]. It should be noted that hyponatremia is not always observed in adrenal dysfunction, since the use of drugs such as sodium bicarbonate, hyperosmolar solutions eliminates true electrolyte imbalance.

To date, there has been no unambiguous laboratory diagnosis for CIRCI. The diagnosis of "primary adrenal insufficiency", largely used in patients at the outpatient stage, often does not provide grounds for making a diagnosis of CIRCI.

Laboratory diagnosis of "primary adrenal insufficiency" is based on the assessment of the level of adrenocorticotropic hormone (ACTH), cortisol, renin and aldosterone in the blood plasma in the early morning hours [6–8]. It is recommended to exclude the diagnosis of "adrenal insufficiency" if the level of cortisol in the blood in the morning is above 500 nmol/l [9]. Fluctuations in the level of cortisol in the blood plasma during CI

development is a dynamic process and cannot be a criterion for assessing the degree of damage to the adrenal glands. In addition, the formation of sepsis and acute respiratory distress syndrome is often associated with dysregulation of glucocorticoid receptors, which, in turn, leads to dysregulation of the transcription of inflammatory markers. This condition is called corticosteroid resistance (corticoresistance) associated with systemic inflammation [10].

If clinical signs of adrenal insufficiency do not meet the above laboratory criteria, diagnostic tests are recommended in the absence of contraindications [11, 12]. A stimulation test is performed with synthetic ACTH preparations (1–24 ACTH) and (or) an insulin tolerance test [13–15]. The diagnostic test with 1–24 ACTH is based on the evaluation of the adrenal response. With an increase in the level of total cortisol in the blood above 500 nmol / l, "primary adrenal insufficiency" can be excluded.

The informativeness of a diagnostic test with synthetic ACTH in assessing the level of total cortisol depends on the level of cortisol-binding protein and, to a lesser extent, on albumin in blood plasma [16, 17]. During CI, especially in sepsis, the blood level of corticosteroid-binding globulin drops by 50%, resulting in an increase in the percentage of free cortisol [18]. In this case, the results of this diagnostic test for the purpose of CIRCI detecting are uninformative. Evaluation of free cortisol levels in the ICU is difficult, as it is not a routine method.

The insulin resistance diagnostic test makes it possible to assess the reactivity of the entire hypothalamic–pituitary–adrenal (HPA) axis. The test is considered to be positive when the glucose level is below 2.2 mmol/l at any of the test points. However, conducting hypoglycemic stress in CI conditions is unsafe and is fraught with deterioration in the severity of the condition [15].

The interpretation of the results of the above methods for assessing the level of hormones and diagnostic tests in order to identify CIRCI is biased. The ability of the adrenal glands to respond to the administration of high doses of synthetic ACTH in the form of an increase in cortisol levels does not determine the adequacy of the HPA axis, namely: there is no information on the response of the HPA axis to stimuli such as hypotension and hypoglycemia. Being exposed to a test with a high dose of synthetic ACTH is not a natural condition for the body, especially during the development of septic shock [19, 20].

The impossibility of interpreting the above results of diagnostic and laboratory tests is also based on completely different fluctuations in the level of ACTH and cortisol in CI (Fig. 1).

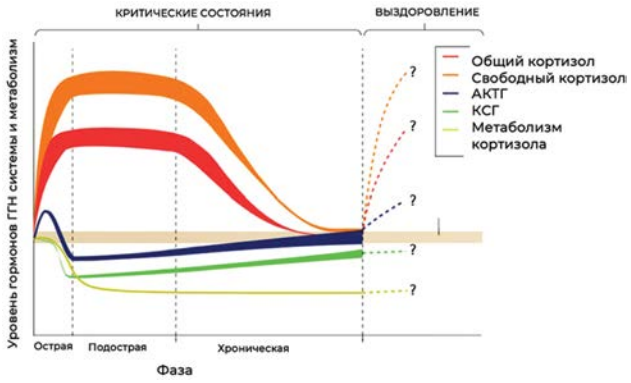

Fig. 1. Hormone level of the hypothalamic pituitary adrenal (HPA) axis and metabolism. Time-dependent and dose-dependent changes in plasma concentrations of the key components during critical illness. The graph shows the dynamic alterations in the blood plasma concentrations of adrenocorticotropic hormone (ACTH), total cortisol, cortisol-binding globulin (CBG) and free cortisol, as well as cortisol metabolism following the onset of critical illness. The acute phase is mostly characterized by a centrally ACTH-driven rise in cortisol; the sub-acute phase is marked by sustained elevated total cortisol and free cortisol but low blood plasma ACTH levels; the chronic phase is a phase during which neither plasma ACTH nor plasma cortisol levels are elevated above normal; and the recovery phase is that in which plasma ACTH and (free) cortisol rise to supra-normal levels that often exceed those present during critical illness. Whether and when the plasma concentration returns to normal values remain unclear

An increase in the level of ACTH and, as a result, cortisol, in the acute phase of CI is characterized by the stress response [21]. According to Greet Van den Berghe [22], if vital functions are not restored within a few days, the CI passes from the acute phase to the subacute one. In the subacute phase of CI, a multidirectional level of blood cortisol is observed against the background of suppressed ACTH level [23]. At the same time, an increasing cortisol level is associated with the fatal outcome [24]. Under these conditions, the interpretation of cortisol and

ACTH results and diagnostic tests do not give an objective picture of the presence / absence of CIRCI. Treating CI patients requires urgent decision-making; waiting for hormonal test results precludes the feasibility of such diagnostic methods.

In CI, a high level of cortisol is not an indicator of the safety of the hypothalamus–pituitary–adrenals–target tissue system, since glucocorticoid resistance is not excluded [10, 25]. The development of tissue-specific glucocorticoid resistance in CI may be due to several factors: glucocorticoid receptor α is the classic glucocorticoid protein and functions as a ligand-dependent transcription factor; the glucocorticoid receptor β is not able to bind to the hormone, is located in the cell nucleus and is a dominant inhibitor of the glucocorticoid receptor α. A high content of glucocorticoid receptor β isoforms against the background of a high concentration of pro-inflammatory cytokines in the cytoplasm can play a key role in the mechanism of development of resistance to glucocorticoids [26]. It can be assumed that this is a key factor in the ineffectively high plasma cortisol levels. The question arises: how does hydrocortisone use in CI against the background of elevated levels of cortisol in the blood have a positive effect in the form of a decreased need for vasopressors.

Based on Russian clinical guidelines, patients in a serious condition with symptoms of "adrenal insufficiency" should first, if possible, take hormone blood tests and, without waiting for the results of laboratory tests, begin treatment with glucocorticoids [27]. These recommendations may play a paramount role in diagnosing and initiating treatment for CIRCI.

In the existing foreign recommendations regarding the diagnostic criteria for CIRCI, there is no unambiguous opinion; no priorities are indicated between assessing the level of total blood cortisol and conducting the ACTH1–24 test. At the same time, the ACTH1–24 test is considered to be more preferable than the hemodynamic response to the administration of hydrocortisone for the diagnosis of CIRCI (conditional recommendation, very low quality of the evidence base) [2]. Consequently, a contradiction arises: the lack of standards in the diagnosis of CIRCI and the abstention from the introduction of hydrocortisone in order to assess the hemodynamic response in favor of diagnostic tests. Other diagnostic possibilities were rejected due to the "inappropriateness of their implementation in an intensive care setting".

USE OF HYDROCORTISONE IN THE INTENSIVE CARE SETTING

One of the main indications for the use of hydrocortisone, which is a natural glucocorticoid, is adrenal insufficiency, since hydrocortisone has the highest mineralocorticoid activity [28]. The mineralocorticoid activity of endogenous cortisol is expressed in the reabsorption of sodium and, as a consequence, water in the renal tubules and excretion of potassium [29]. In addition, cortisol increases sensitivity to vasopressor agents such as catecholamines and angiotensin II in vascular smooth muscle. These effects are mediated in part through increased transcription and expression of appropriate endothelial receptors. Unlike natural, there are synthetic glucocorticoids, namely: non-fluorinated (prednisolone, prednisone, metiprednisolone) and fluorinated (dexamethasone, betamethasone, triamcinolone). The main difference between natural and synthetic glucocorticoids is the predominance/absence of mineralocorticoid activity. In the absence of hydrocortisone and the need to replace the function of the adrenal glands, the use of non-fluorinated (prednisone, prednisolone, methylprednisolone) glucocorticoids is allowed. Fluorinated glucocorticoids have practically no mineralocorticoid activity, and therefore their use to stabilize hemodynamics is not recommended [28].

If the mineralocorticoid activity of hydrocortisone is not sufficient, fludrocortisone, which has a high mineralocorticoid activity, is used.

The Cochrane meta-analysis "Glucocorticoids in the treatment of sepsis", published in 2018, included data from 15 studies demonstrating the benefit of using hydrocortisone in CI [30]. The table below summarizes the results of the Cochrane analysis, taking into account the use of hydrocortisone or other glucocorticoids (Table 1) (bold type indicates the use of hydrocortisone).

Table

Results of Cochrane meta-analysis. Glucocorticoids in the treatment of sepsis (Review)

Authors	**Group on glucocorticoid treatment, n/N** **Control, n/N**									
	1	2	3	4	5	6	7	8	9	10
***Bollaert* 1998 [31]**	**7/22** 12/19		**7/22** 12/19			**3/8** 6/9	**8/22** 12/19	**15/22** 4/19	**15/21** 7/19	**1/22** 3/19

***Briegel* 1999 [32]**	**3/20** 4/20		**3/20** 4/20				**4/20** 6/20	**17/20** 12/20	**18/20** 16/20	**1/20** 0/20
Bone 1987 [33]		65/191 48/190								
Luce 1988 [34]		22/38 20/37								18/37 16/36
***Chawla* 1999 [35]**	**6/23** 10/21		**6/23** 1021				**6/23** 8/21	**16/23** 9/21	**17/23** 10/21	**1/23** 2/21
***Annane* 2002 [36]**	**82/151** 92/149		**82/151** 92/149			**60/114** 73/115	**90/151** 101/149	**60/151** 40/149	**67/151** 57/149	**11/51** 8/149
***Oppert* 2005 [37]**	**10/23** 11/25		**10/23** 11/25			**5/12** 6/14		**14/18** 16/23		
***Confalonieri* 2005 [38]**	**0/23** 6/23				**0/23** 6/23		**0/23** 7/23			**1/23** 1/23
***Tandan* 2005 [39]**	**11/14** 13/14		**11/14** 13/14			**11/14** 13/14			**5/14** 3/14	
***Rinaldi* 2006 [40]**	**6/26** 7/26	**6/26** 7/26					**5/26** 6/26			
Cicarelli 2007 [41]	7/14 12/15									0/14 0/15
Meduri 2007 [42]	10/42			10/42 8/19		5/10 3/6	11/42 10/19			0/42 0/19
***Sprung* 1984 [43]**			**33/43** 11/16							**1/43** 2/16
***Hu* 2009 [44]**	**4/38** 6/39		**4/38** 6/39				**4/38** 6/39	**33/38** 27/39		
Snijders 2010 [45]	6/104 6/109				6/104 6/109					0/104 0/109
***Arabi* 2011 [46]**	**33/39** 26/36		**33/39** 26/36				**24/39** 24/36	**24/39** 14/36		**13/39** 4/36
Yildiz 2002 [47]	8/20 12/20	8/20 12/20				2/5 5/9				0/20 0/20
Yildiz 2011 [48]	16/27 15/28	16/27 15/28				3/6 8/14				0/27 0/28
Meijvis 2011 [49]	9/151 11/153				9/151 11/53					1/151 0/153
***Sabry* 2011 [50]**	**2/40** 6/40				**2/40** 6/40		**2/40** 6/40	**38/40** 26/40		**2/40** 2/40
***Liu* 2012 [51]**	**3/12** 6/14			**3/12** 6/14						
Rezk 2013 [52]	0/18 3/9			0/18 3/9						+
***Gordon* 2014 [53]**	**7/31** 7/30		**7/31** 7/30				**7/31** 8/30	**19/31** 13/30	**23/31** 21/30	**0/31** 0/30
Torres 2015 [54]	6/59 9/61				6/59 9/61		1/42 6/46			
VASSCSG 1987 [55]		23/112 24/111								14/112 10/111
Schumer 1976 [56]			9/86 33/86							2/86 1/86
***Sprung* 2008 [57]**	**86/251** 78/248		**86/251** 78/248			**49/125** 39/108	**102/251** 89/247	**186/251** 145/248	**200/251** 183/248	**15/234** 13/232
p	0.013	0.3	0.03	0.013	0.06	0.09	0.045	0.00001	0.01	0.4

Notes: n — number of deaths; N — total number of patients. Studies using hydrocortisone are highlighted in bold. 1. 28-day hospital mortality rate of patients with sepsis in case of long course of treatment with low doses of glucocorticoids (n). 2. The effect of glucocorticoids on 28-day hospital mortality rate of patients with sepsis (n). 3. The effect of glucocorticoids on 28-day hospital mortality rate of patients with septic shock (n). 4. The effect of glucocorticoids on 28-day hospital mortality rate of patients with sepsis and ARDS (n). 5. The effect of glucocorticoids on 28-day hospital mortality rate of patients with sepsis and community-acquired pneumonia (n). 6. The effect of glucocorticoids on the 28-day hospital mortality rate of patients with CIRCI (n). 7. Mortality in the intensive care unit. 8. Reversibility of shock for up to 7 days in case of long course of treatment with low doses of glucocorticoids (n). 9. Reversibility of shock up to 28 days in case of long course of treatment with low doses of glucocorticoids (n). 10. Side effects of glucocorticoids: gastroduodenal bleeding, superinfection, hyperglycemia, hypernatraemia, neuromuscular weakness (no significant differences were found in total) (n)

According to the data mentioned in the table, there was a statistically significant reduction in 28-day mortality with long-term use of low doses of glucocorticoids.

The results of the meta-analysis in total did not show a reduction in 28-day mortality with the prescription of glucocorticoids in sepsis. However, analyzing the data, we must certainly take into account both the heterogeneity of the groups and study designs, as well as the heterogeneity of the prescribed drugs - for example, out of 6 studies included in the analysis, only one study used hydrocortisone.

In a subsequent analysis that took into account the distribution of prescribed drugs, 12 studies showed a reduction in 28-day mortality from septic shock with the use of glucocorticoids. Of the 12 studies, 11 were performed using hydrocortisone. Most likely, we can state that there are individual differences in the effectiveness of drugs prescribed for sepsis, and give preference to hydrocortisone, as the most effective of them and having the greatest positive effect on patient survival.

Also, the results of the meta-analysis showed a statistically significant decrease in 28-day mortality in a subgroup of patients who experienced the manifestation of acute respiratory distress syndrome against the background of sepsis. It should be noted that only in one out of three studies presented in the meta-analysis hydrocortisone was prescribed. There was no difference in 28-day mortality in sepsis against the background of the course of severe community-acquired pneumonia without the development of respiratory distress, while out of five studies with the hydrocortisone prescription, only two studies were performed.

The meta-analysis did not show a reduction in 28-day mortality in groups where patients were considered to develop CIRCI during glucocorticoid therapy. This is probably due to the selection of the groups (out of 8, hydrocortisone was used in five studies). These results cannot be taken unequivocally, since CIRCI development is a common CI consequence, and its occurrence can be considered in the remaining 11 studies, where patients with sepsis were treated with hydrocortisone.

The use of glucocorticoids showed a decrease in mortality in patients treated in the intensive care unit (11 out of 13 studies used hydrocortisone).

Objectively, we understand that this result of the meta-analysis when prescribing glucocorticoid therapy is perhaps the most important. This is due to the greatest severity of the condition of patients treated in intensive care units; it is this cohort that should be considered as true patients with the development of multiple organ failure against the background of sepsis, including those requiring replacement of vital functions. Since CIRCI pathophysiologically shapes the course of subacute and chronic stages of CI, it is these patients who are treated in ICUs for the longest time; and the most prioritized result is a statistically significant reduction in mortality in these groups, rather than an overall effect on mortality in all patients diagnosed with sepsis based on the broader diagnostic definitions adopted in the early years of the concept of systemic inflammatory response syndrome (SIRS). A large number of these patients, due to moderate (albeit advantageous in terms of early alertness and escalation of treatment strategy) overdiagnosis of sepsis, did not have a severity of the condition that would require a stay in ICUs for treatment. Therefore, they did not experience the development of CIRCI which is characteristic of the subacute stage of the CI.

There was a statistically significant increase in the reversibility of septic shock both within 7 and 28 days with long-term use of low doses of hydrocortisone - in 10 and 7 studies, respectively.

The severity of the patients' condition, as assessed by the Sequential Organ Failure Assessment (SOFA) Score, statistically significantly decreased with the use of glucocorticoids (hydrocortisone was used in 7 out of 8 studies).

In total, there were no statistically significant differences in the side effects of glucocorticoids.

Overall, the key conclusion from the meta-analysis is that the best results with glucocorticoids in septic patients were achieved in situations where the initial severity of the condition was extreme, patients required treatment in the ICU, had significant manifestations of respiratory and cardiovascular insufficiency, primarily respiratory distress syndrome and septic shock. These results are in very good agreement with the concept of CIRCI development in the subacute and chronic stages of CI and the need to prescribe glucocorticoid replacement therapy in this situation. An important confirmation of this conclusion is the fact that all the demonstrated survival preferences of patients treated with glucocorticoids were observed precisely in the groups of patients and studies where drugs (mainly hydrocortisone) were prescribed for a long course and at low doses. Short courses of corticosteroids at higher doses did not demonstrate any benefits, which most likely confirms their importance not

as drugs stabilizing hemodynamics in the acute stage of CI, but as a means of long-term replacement therapy in the subacute and chronic stages of CI.

International guidelines for management of sepsis and septic shock in adults 2021 for the first time proposed the administration of hydrocortisone to patients in septic shock, without waiting for the maintenance of normovolemia. In addition, with persistent unstable hemodynamics, the initiation of hydrocortisone administration is recommended 4 hours after the administration of noradrenaline or epinephrine at a dose of up to at least 0.25 μg/kg/min [29, 58–60]. In the 2016 recommendations, the prescription of hydrocortisone occurred in the presence of persistent hemodynamic instability against the background of the maintenance of normovolemia and high doses of vasopressors. It was also suggested that hydrocortisone should be avoided in septic patients without septic shock [61].

In contrast to the above, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in their 2017 recommendations suggested the use of hydrocortisone in the early stages, before the development of multiple organ failure, for CIRCI in patients with severe community-acquired pneumonia and circulatory arrest [30, 62–64]. In severe community-acquired pneumonia, the use of hydrocortisone can shorten the period of hospitalization, the duration of mechanical ventilation, prevent acute respiratory distress syndrome and reduce mortality.

It is not recommended to administer hydrocortisone to patients with sepsis and the need for vasopressors: hydrocortisone has no effect on preventing the development of septic shock, does not reduce the length of stay in the ICU and mechanical ventilation [30]. The ineffectiveness of hydrocortisone in sepsis is probably due to: its late administration to the patient against the background of the development of severe cortico-resistance; use of glucocorticoids other than hydrocortisone.

To date, there have been no guidelines for the diagnosis and treatment of CIRCI in patients undergoing ECMO. However, by analyzing the pathophysiological changes, both directly occurring during ECMO and preceding it, we can extrapolate the data obtained in CI. According to Greet Van den Berghe, CI already implies such a degree of organ damage and adrenal dysfunction that by the time ECMO is indicated, we must certainly talk about the development of a subacute phase of CI. Therefore, in the next section, we are going to consider the pathophysiological changes during ECMO and the potential mechanisms for CIRCI development.

EXTRACORPOREAL MEMBRANE OXYGENATION IN THE SUB-ACUTE PHASE OF CRITICAL ILLNESS

Against the background of the development of multiple protective neuroimmunoendocrine responses, when CI occurs, SIRS is formed. The trigger mechanism for the development of SIRS in CI is an increase in the level of damage-associated molecular patterns (DAMPs) and (or) an increase in the level of pathogen-associated molecular patterns (PAMPs) [65, 66]. The neuroimmunoendocrine response in CI is formed by integrating the influx of information from the vagus nerve, peripheral cytokine interactions with receptors in the region of the organs surrounding the ventricles of the brain (the vascular organ of lamina terminalis, subfornical organ, median eminence, neurohypophysis, subcommissural organ and area postrema), brain vessels and local production of cytokines within the central nervous system [67–69]. According to Greet Van den Berghe [70], if vital functions are not restored within a few days, CI passes from the acute phase to the subacute one. The transition to the subacute phase of the CI and the depletion of the protective stress response are the result of damage to the nuclei of the limbic, hypothalamic, noradrenergic and autonomic systems.

As a consequence of diverse pathophysiological changes in CI, a syndrome of multiple organ failure (MOF) is formed. Management of CI and MOF due to various reasons is the main task of modern resuscitation. In intensive care, various methods of treatment are used, including those characterized by high aggressiveness. ECMO in patients with severe respiratory and (or) heart failure has an independent additional effect on the functioning of organs and systems. ECMO is a very invasive therapy and is accompanied by the introduction of synthetic materials into the vascular bed and constant contact of blood with an artificial circulation circuit, which, in turn, aggravates the patient's already serious condition and is an independent factor in the development of a cascade of inflammatory reactions [71]. Often, this group of patients undergo ECMO for a long time, which can lead to typical complications of extracorporeal methods, namely: hypoxemia, impaired blood coagulation, infectious complications, and organ dysfunction syndrome [72].

Unstable hemodynamics and the need for vasopressors during ECMO may be characterized not only by medullary, but also by cortical dysfunction, since this is a single organ - the adrenal glands. This reasoning is

based on the fact that during the stress response, the limbic system through the sympathetic nervous system regulates the release of catecholamines in the adrenal medulla. Simultaneously, the HPA axis is activated [73]. That is, one of the manifestations of the depletion of the stress response of the neuroendocrine system in CI can be attributed simultaneously to the dysfunction of the nervous (brain layer) and humoral (cortical layer) regulation of the adrenal glands. That is, both dysfunction of the nervous (medulla) and humoral (cortex) regulation of the adrenal glands can be attributed to one of the manifestations of the depletion of the stress response of the neuroendocrine system in CI.

During ECMO, not only different groups of drugs are used, but their doses and duration of administration are also increased. The use of propofol, benzodiazepines, and barbiturates increases the sensitivity of gamma-aminobutyric acid receptors (GABA) to the GABA mediator and leads to inhibition of brain activity [74], which, in turn, can cause suppression of HPA axis activity [75]. In addition, the use of selective α2-adrenergic agonists with a wide range of pharmacological properties, which have become especially popular recently, suppresses the activity of the locus coeruleus of the brainstem [74]. The noradrenergic system regulates, in addition to the level of consciousness, the functional activity of the hypothalamus during the stress response [68, 75]. In other words, drugs for general anesthesia and sedation inhibit brain activity, which leads to suppression of the body's stress response in CI. Therefore, even in case of forced administration of the above drugs, including for ECMO, the doctor must clearly understand the degree of inhibition of the function of the neuroendocrine system mediated by their use.

Thus, ECMO in severe respiratory and (or) heart failure is an additional aggressive factor in CI, which in turn requires consideration of CIRCI.

In the existing recommendations and in a number of scientific papers on the use of hormone replacement therapy with hydrocortisone in the ICU, patients on ECMO are not considered.

CONCLUSION

Adrenal dysfunction caused by critical illness is a dynamic process and can develop at any time during intensive care. Crisis-induced adrenal dysfunction is characterized by reduced cortisol production and/or resistance of target tissues to cortisol.

Assessment of the level of adrenocorticotropic hormone, cortisol, renin, aldosterone in the blood and diagnostic tests in critically ill patients are not informative. The identification of adrenal dysfunction caused by critical illness should be based primarily on the clinical assessment of the patient and the need for vasopressors.

The use of hydrocortisone as a “treatment of despair” in septic shock against the background of resistance to vasopressors and normovolemia more likely discredits hydrocortisone. There are high chances that it is the imbalance between pro- and anti-inflammatory markers and the increase in blood cortisol levels observed in septic shock that characterize the presence of adrenal dysfunction caused by critical illness. It is possible that the reason for the ineffectiveness of hydrocortisone administration in sepsis is due to the late start of its use and, as a result, the continued aggravation of the severity of the patient's condition.

The Cochrane meta-analysis "Glucocorticoids in the treatment of sepsis" showed that survival was higher among those patients with respiratory distress syndrome and septic shock who received glucocorticoids (mainly hydrocortisone) for a long course and at low doses.

These results are in very good agreement with the concept of the development of adrenal dysfunction in the subacute and chronic stages of critical illness, and the need for glucocorticoid therapy in this situation is considered.

Recommendations for hydrocortisone administration in severe community-acquired pneumonia and circulatory arrest suggest that the use of this drug should also be considered when performing extracorporeal membrane oxygenation. Long-term use of drugs for general anesthesia and sedation during extracorporeal membrane oxygenation has a negative effect on stress reactions from the central nervous system, in particular, hypothalamic-pituitary activity is suppressed.

The timing of hydrocortisone administration to critically ill patients requiring extracorporeal membrane oxygenation and the duration of this therapy is currently a topical issue in intensive care.

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