**Review**
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# The Role of Extracorporeal Membrane Oxygenation in the Complex Treatment of Acute Chemical Poisoning

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**AIM OF STUDY** Analysis of literature data on the use of extracorporeal membrane oxygenation in acute chemical poisoning.

**MATERIAL AND METHODS** The search for domestic publications was carried out in the Elibrary database, foreign publications — in the MEDLINE / PubMed, Google Scholar databases for the period of 2010–2023. The terms used as a search query were according to the official MeSH terms: "Extracorporeal Membrane Oxygenation" OR "Membrane Oxygenation, Extracorporeal" OR "ECMO Treatment" AND "poisoning".

**RESULTS** This review provides information on the outcomes of the use of veno-arterial and veno-venous extracorporeal membrane oxygenation (ECMO) for refractory cardiogenic shock, cardiac arrest and severe ARDS in acute chemical poisoning.

**CONCLUSION** Data analysis showed that in patients with acute chemical poisoning, the incidence of complications and mortality was lower when ECMO/ECMO-CPR was included in the complex therapy compared with patients in whom other reasons (not related to acute poisoning) served as indications for the use of this technique. This is probably due to the fact that patients in the group with acute poisoning are younger, they have fewer concomitant diseases; and ECMO is required, as a rule, for a shorter period of time before the toxicant is eliminated from the body using the methods of their elimination and restoration of disturbed functions.

**Keywords:** acute poisoning, toxicology, extracorporeal membrane oxygenation, ECMO, ECPR, VAECMO, VVECMO, acute poisoning of chemical etiology
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AP - acute poisoning
CPR - cardiopulmonary resuscitation
ECMO - extracorporeal membrane oxygenation
VA - veno-arterial
VV – veno-venous

## RELEVANCE

Acute poisoning (AP) can lead to life-threatening complications and even death due to cardiac and/or respiratory failure [1, 2]. The development of cardiogenic pulmonary edema is usually caused by an overdose of substances that either inhibit contractility directly, exerting a negative inotropic effect, or increase pre- and afterload [1]. This is typical for poisoning by calcium antagonists or beta-blockers; other substances, such as H1-blockers, phenothiazines, antiarrhythmic drugs, local anesthetics and plant poisons, also have a negative inotropic effect [1–5]. Often the cause of hemodynamic disturbances is not the direct effect of xenobiotics on the cardiovascular system, but the result of the development of hypoxia, acidosis, hypovolemia and arrhythmia. Overdose of a number of drugs can lead to the development of myocarditis and heart failure [6–9]. Cardiogenic shock can occur because of poisoning by carbon monoxide, cyanide, and pesticides due to mitochondrial dysfunction [10, 11].

Severe respiratory failure can develop as a result of ventilation-perfusion mismatch, a decrease in the diffusing capacity of the lungs (pneumonia, inhalation of toxic gases, etc.) and the development of acute lung injury (after administration of naloxone, opioids, salicylates, phosgene, etc.) [12–15].

Extracorporeal membrane oxygenation (ECMO) is an invasive extracorporeal method that provides temporary replacement of circulatory and respiratory function while a patient with AP undergoes a set of measures, including, among other things, methods for accelerating the elimination of toxic substances [16]. In recent years, ECMO/ECMO-CPR (cardiopulmonary resuscitation) has become widely used in the treatment for refractory cardiogenic shock and acute respiratory distress syndrome (ARDS), including various etiologies and refractory clinical death [17].

Modern data also indicate the more frequent use of ECMO/ECMO-CPR these days for acute exotoxicosis throughout the world [16, 18]. Thus, in the USA, according to Gummin D.D., ECMO for acute poisoning of chemical etiology was used in 141 cases in 2019 [19]. The wider use of ECMO is likely due to optimization of approaches to ECMO, increased availability, and improved awareness of severe patients who require this technique.

**Aim:** analysis of literature data on the use of extracorporeal membrane oxygenation in acute chemical poisoning.

## MATERIAL AND METHODS

The search for domestic publications was carried out in the eLibrary database, foreign - in the MEDLINE/PubMed, Google Scholar databases for the period of 2010–February 2023. The search terms used were according to the official MeSH terms: “Extracorporeal Membrane Oxygenation” OR “Membrane Oxygenation, Extracorporeal” OR “ECMO Treatment” AND “poisoning”. The analysis included articles that presented the outcomes of the use of ECMO in acute chemical poisoning: descriptions of individual cases, series of clinical observations, expert opinions and retrospective cohort, prospective observational studies.

### EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO is a temporary method of circulatory support to maintain homeostasis by partially/completely replacing the gas exchange function of the lungs (oxygenation, elimination of carbon dioxide) and/or the pumping function of the heart in case of the development of non-life-threatening disorders of systemic hemodynamics and (or) pulmonary gas exchange [16, 20]. ECMO is not a treatment method; its use allows temporary replacement of circulatory and respiratory function. ECMO technology is aimed at supporting patients who are in critical condition, but at the same time with potentially reversible disorders of the respiratory and (or) cardiovascular system, the treatment of which is ineffective using traditional methods of intensive care [16, 20].

The following ECMO techniques exist: veno-venous, veno-arterial (Fig. 1). ECMO connection options (peripheral): veno-venous (VV) - “femoral vein-jugular vein”, “femoral vein-femoral vein”; veno-arterial (VA) - “femoral vein-femoral artery”, “femoral vein-subclavian artery” (cannula or graft); combined (hybrid) version - “femoral vein, femoral artery-jugular vein” [16, 21, 22].

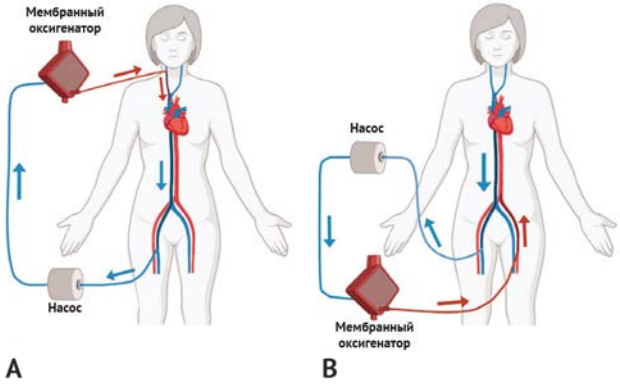


Figure. Methods of extracorporeal membrane oxygenation [16]. A — veno-venous; B — veno-arterial

#### CONTRAINDICATIONS TO THE USE OF ECMO

Contraindications are divided into absolute and relative. Most contraindications are relative, related to the balance between the risk of ECMO and the potential benefit of the intervention. Absolute contraindications are as follows: premorbid background of incurable diseases and futility of treatment (damage to the central nervous system, oncology with metastatic lesions), extensive hemorrhagic stroke, impossibility of vascular cannulation due to thrombosis, unwitnessed cardiac arrest, prolonged CPR without adequate tissue perfusion and aortic dissection [18, 23, 24]. Relative contraindications are as follows: restrictions on anticoagulant therapy, old age, obesity, inability to provide blood components. Relative contraindications vary depending on the experience of the individual institution, the ECMO team and local protocols [16, 24].

#### COMPLICATIONS DURING ECMO

According to the Extracorporeal Life Support Organization (ELSO) registry [23], complications during ECMO are divided into: a) hemorrhagic - in 20% of cases; b) thromboembolic (due to circuit thrombosis); c) infectious and d) complications associated with cannulation, for example, limb ischemia, perforation, vessel dissection, etc. [25–27].

The purpose of using ECMO in patients with acute chemical poisoning is to temporarily maintain lung and/or heart function in the event of severe respiratory and/or heart failure during detoxification with the aim of eliminating toxic substances up to their removal from the body and restoring the functions of damaged organs [16].

#### THE USE OF VENO-ARTERIAL ECMO IN PATIENTS WITH ACUTE CHEMICAL POISONING

A retrospective study of the use of VA ECMO in patients with cardiogenic shock in AP in the period of 2003–2018 was conducted. According to the ELSO registry, 104 cases of the use of this technique in AP have been registered [28]. An assessment of the frequency of VA ECMO use in AP showed an increase in the latter in previous years. The median age was 34 years, 53.5% were men. In 47.1% of cases, the reason for VA ECMO was poisoning by cardiotoxic drugs, opiates took second place - 8.7%, cocaine (3.8%) and antidepressants (3.8%) took third place. Before the start of VA ECMO, 85% of patients were prescribed at least 2 vasopressor/inotropic drugs, 33% (n=34) had cardiac arrest and CPR. Within 24 hours after connecting VA ECMO, pronounced positive dynamics of hemodynamic parameters, as well as pH and serum bicarbonate levels were observed. The median duration of VA ECMO was only 68 (48;113) hours. 55 patients (52.9%) were discharged from the hospital in satisfactory condition; in 47% of cases, patients with recorded cardiac arrest before the start of VA ECMO-CPR survived.

Also, a large-scale retrospective study was conducted to evaluate the effectiveness of the use of VA ECMO in AP in the period of 2000–2018, which included 332 adults and 75 children [29]. Data from 55 US poison control

centers were analyzed. The most common use of VA ECMO was required in patients with poisoning by sedative/hypnotic drugs (26%), antidepressants (25%), calcium channel blockers (19%), and opioids (17%). In children, VA ECMO was used in hydrocarbon (37%), antiarrhythmic (15%), or antihistamine (8%) poisoning. Mortality was 29.5% in adults, 32% in children. 43% of 111 patients survived after cardiac arrest. The authors noted that mortality was similar in poisoning by various toxic substances.

It should be emphasized that to date there are no randomized controlled studies examining the effectiveness of ECMO in AP. However, several retrospective studies provide insight into survival between groups of patients treated with VA ECMO compared with standard care. Thus, Masson, Romain, et al. analyzed 62 patients (52 with refractory shock, 10 with persistent cardiac arrest) who were hospitalized in different hospitals with the possibility (or lack thereof) of ECMO use in the period of 1999–2010 [30]. The average age of the patients was 48±17 years. The complex of treatment of one group of patients included VA ECMO, while the second group, accordingly, received standard treatment. The largest group consisted of patients with poisoning by antiarrhythmic drugs. Poisoning by three toxicants was diagnosed in 45 cases. The authors indicated that the groups were comparable. Patients treated with VA ECMO had significantly better survival compared with the other group (86% vs 48%, respectively; odds ratio for mortality: OR=0.15 [0.02–0.85]). This trend persisted in analyzes adjusted for severity of critical illness and toxic agent (aOR=0.18 [0.03–0.96]). It is noteworthy that not a single patient with cardiac arrest in the group without ECMO-CPR survived, unlike all survivors in the other group (n=3). Patients with ß-blocker poisoning had lower mortality (p=0.02). The median duration of VA ECMO was 6 days. The following complications were observed in the ECMO group: 4 patients developed limb ischemia, 2 of whom required surgical revascularization, and 2 had severe bleeding at the cannulation site.

A study by Mégarbane Bruno et al. showed that out of 17 patients who were treated with VA ECMO-CPR for refractory cardiac arrest (12 with acute chemical poisoning – Group I, 5 for other reasons – Group II), survival rate in AP was 25% (n=3) versus 0% in the other group [31]. At the same time, the patients were much older in Group I; the groups were comparable in other indicators (median maximum SOFA score during hospital observation (18.5 (15.8; 20.3) vs. 18.0 (17; 20)); median duration from cardiac arrest to cannulation (120 minutes (45; 180) vs. 135 minutes (120; 185)). The median duration of VA ECMO in patients with AP was 56 (5; 108) hours. It is noteworthy that in surviving patients with AP, cardiac arrest before the start of ECMO lasted 30, 100 and 180 minutes; they were discharged in satisfactory condition on the 12th, 13th and 14th days after hospitalization; no neurological deficits or cardiovascular complications were subsequently noted.

Another retrospective cohort study found similar results. 64 patients receiving VA ECMO/VA ECMO-CPR were examined, 19 of them with AP. Survival of patients with AP was significantly higher compared with patients undergoing VA ECMO for other reasons (79% vs. 20%, respectively, $p < 0.0001$, statistically significant); multivariate analysis showed that poisoning was significantly associated with lower odds of mortality (aOR=0.07 [0.01–0.28]). Patients with AP who received VA ECMO for refractory cardiac arrest had a survival rate of 67% versus 9% in undergoing VA ECMO patients with refractory cardiac arrest not related to poisoning [32].

The results of the previous study demonstrated not only a high survival rate of patients whose treatment included the use of VA-ECMO/VA ECMO-CPR due to AP (76%), but also a faster neurological recovery with complete restoration of cardiac activity [33]. The relatively high survival rate without neurological deficit of patients with AP on VA ECMO, despite the prolonged cardiac arrest before cannulation, contrasts with the very low survival of patients from the other group with refractory cardiac arrest for other reasons [34].

According to an observational retrospective study by Matteo Pozzi M.D. et al. between 2007 and 2020, 32 patients (mean age 45.4±15.8 years; 62.5% women) were treated with VA ECMO/VA ECMO-CPR for refractory cardiogenic shock caused by drug intoxication (n =25) or cardiac arrest during AP (n= 7) [35]. 7 (21.8%) patients developed lower extremity ischemia during the VA ECMO procedure itself. The authors explain the high level of development of this complication by the need to use high doses of vasopressor drugs in case of poisoning by cardiotoxic drugs. The incidence of other complications was consistent with the results of other studies [36, 37]. The leading infectious complication was pneumonia (n=12; 37.5%). In 26 cases (81.2%), patients were successfully weaned off VA ECMO after an average of 2.9 ± 1.3 days. One patient (3.1%) died after being disconnected from VA-ECMO due to multiple organ failure; and survival before hospital discharge was 78.1% (n = 25), and no neurological deficits were noted in those patients. This is consistent with the previous studies [30]. There were no statistically significant differences in survival rate depending on gender (men - 75.0% versus women - 80.0%; p = 0.535), type of poisoning (single drug - 81.8% versus multiple drugs - 76.1%; p =0.544), and the hospital where VA

ECMO was performed. Survival was significantly lower in patients receiving VA ECMO during ongoing CPR (42.8% vs. 88.0%; p = 0.026, statistically significant). The median duration of treatment in the intensive care unit and in the hospital was 9 and 18 days.

Duburcq Thibault et al., based on the results of their study, concluded that reducing the time from hospitalization to the start of VA ECMO is one of the key points in the outcome of the disease. An analysis of the results of treatment of 22 patients with drug poisoning who required the use of VA ECMO showed that the time from hospitalization to the start of ECMO was statistically significantly shorter in surviving patients, the survival rate was 45.4% (10 of 22) [38].

Anita Orlando et al. described a case of successful VA ECMO use in the development of cardiogenic shock due to severe ethylene glycol (EG) poisoning. The controversial point in this case was the installation of introducers in advance against the background of progressive deterioration of the patient's condition, without waiting for the perfusionist. Chemical and toxicology testing showed the concentration of EG in the blood - 32.2 mg/dl, in urine - 160 mg/dl (lethal doses). The patient underwent hemodialysis. VA ECMO was connected as indicated. After 6 hours, a decrease in the level of EG in the blood (to 8.2 mg/dL) was observed. The duration of VA ECMO was only 16 hours, after 24 days the patient was discharged in satisfactory condition [39].

A large retrospective study was also conducted in Japan. A total of 5263 patients were enrolled and treated with VA ECMO between 2010 and 2013 as a result of cardiogenic shock or cardiac arrest. Of these, 90 people were with AP. The overall mortality rate was 72.5%, the lowest was in the group of patients with AP - 62% [40].

A number of other studies have been conducted and clinical observations have been described, demonstrating the positive effect of including VA ECMO in complex therapy on the outcome of the disease in patients with poisoning by various toxic substances (aluminum phosphide, mushrooms, plant poisons, etc.) [41–46].

Based on the results of the studies, individual or case series, it can be concluded that patients who received VA ECMO/VA ECMO-CPR for refractory shock and cardiac arrest due to AP had significantly lower mortality than patients who underwent VA ECMO/VA ECMO-CPR because of other reasons (acute coronary syndrome, pulmonary embolism, etc.).

#### USE OF VV ECMO IN ACUTE CHEMICAL POISONING

VV ECMO should be used for severe acute respiratory distress syndrome (ARDS). The criteria for starting ECMO are as follows: pO2/FiO2 less than 80 mmHg (with PEEP above 15 mbar), pH less than 7.2, and the lung injury score (LIS) of more than 3 points [24].

Radowsky Jason S. et al. conducted a retrospective study in order to comparatively evaluate the effectiveness of ECMO in patients with various diseases, including AP [47]. The study included 189 patients, 27 of whom (14%) were diagnosed with AP. Patients with AP who required VV ECMO were younger, had lower mean body mass index and pO2/FiO2, and higher Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) scores than patients without AP (p=0.002, 0.01, 0.03 and 0.01, respectively, statistically significant). There were no differences in precannulation pH, lactate, and Sequential Organ Failure Assessment (SOFA) scores between the two groups (p=0.24, 0.5, 0.6, respectively). This study demonstrated no difference in survival between the groups (p=0.95). Among the patients with a favorable outcome, there was no difference in the duration of ECMO and hospitalization (p=0.24, p=0.07).

An earlier study analyzed data from the ELSO registry. Overall mortality was 41% in an analysis of a cohort of 83 patients who underwent ECMO in AP. In 56% of cases, VV ECMO was used [48]. Patients who underwent ECMO for aspiration pneumonia or inhalation injury had the highest survival rate - 89%.

Krugliakova N.M. et al. presented a case of using VV ECMO for inhalation poisoning by hydrofluoric acid. The authors pointed out the effectiveness and promise of this method in the complex treatment for acute poisoning [49].

Data analysis showed that the clinical outcomes of using ECMO/ECMO-CPR in patients with acute chemical poisoning are significantly better compared to patients in whom other reasons were indications for the use of ECMO/ECMO-CPR (lower incidence of complications, mortality rate). This is probably due to the fact that patients with acute poisoning are younger, have fewer concomitant diseases, and in their case ECMO is required, as a rule, for a shorter period of time – until removing the toxicant from the body using methods for their elimination and restoration of impaired functions.

Recommendations for ECMO in patients with acute chemical poisoning:

Cameron Upchurch et al. and other researchers, based on their research results, formulated the following indications for the use of ECMO in cases of acute chemical poisoning in the absence of contraindications [16]:

1. VA ECMO is indicated for refractory cardiogenic shock in patients with acute chemical poisoning, despite the treatment performed (infusion therapy, administration of vasopressors/inotropic drugs, antidote therapy, administration of high doses of insulin, fat emulsions, etc.) [50].
2. In patients experiencing cardiac arrest, immediate consideration of the possibility of installing VA ECMO-CPR is indicated.
3. The indication for the use of VV ECMO in acute chemical poisoning is the development of severe ARDS according to standard indications [51, 52].

In a study by St-Onge, Maude et al., the economic component of the use of VA ECMO in patients with acute poisoning by cardiotoxic drugs was analyzed. It is likely that the use of VA ECMO is a cost-effective treatment method, however, the authors noted the limitations of the study - the data were based on a small sample and required confirmation in subsequent research [53].

There is an opinion among some experts that ECMO is not safe during therapy with fat emulsions in cases of poisoning by fat-soluble toxicants, such as propranolol, verapamil, some antidepressants, etc. [54, 55]. This is explained by the high risk of thrombus formation in the circuit as a result of lipid agglutination, despite heparinization. Such reports are rare [56]. Whereas, on the contrary, the results of numerous observations show successful experience in the simultaneous use of ECMO and fat emulsions [57–62].

In case of poisoning by dialysable poisons, the simultaneous use of hemodialysis with ECMO should be considered to more quickly eliminate toxic substances and reduce the duration of ECMO [16].

Adeel Abbasi M.D. et al. raise the question of the ethical issues of providing ECMO to patients with mental illness. The authors emphasize that if there are indications for ECMO in patients with AP of chemical etiology, taking a toxic substance for the purpose of suicide, drug/alcohol intoxication, or the presence of a mental illness should not be considered a contraindication for ethical reasons [63].

ECMO can be used as a "bridge" to organ transplantation. In the literature, there are descriptions of observations when lung or heart transplantation was performed in patients with AP on ECMO. For example, a patient with aconitine poisoning who developed severe myocardial necrosis was placed on VA ECMO and underwent heart transplantation 21 days later [64]. A case of using VV ECMO as a “bridge” to lung transplantation in paraquat poisoning is also presented [65].

In acute poisoning by certain toxicants, ECMO may likely be ineffective [16]: in case of poisoning by poisons that cause mitochondrial dysfunction (dinitrophenol, fluoroacetate, cyanide, etc.), interfere with the transport of oxygen to the cell (poisons that cause hemolysis, etc.), contribute to the development of severe coagulopathy and disseminated intravascular coagulation (DIC) syndrome and irreversible damage to target organs (corrosive substances, mercury). The authors note that these are not absolute contraindications to the use of ECMO, but the potential risks and benefits must be carefully weighed. This requires the opinion of a multidisciplinary team after assessing the risk and prognosis [16].

ECMO is a resource-intensive technique, and its effectiveness largely depends on the equipment of the department, its workload, experience and motivation of the staff.

## CONCLUSION

Acute exotoxicosis can lead to life-threatening complications and even death due to cardiac and (or) respiratory failure. Despite the fact that ECMO has been increasingly used in recent years in the intensive care for critical conditions, in acute poisoning of a chemical etiology this technique is still used quite rarely and is not a standard procedure for the treatment of refractory shock/cardiac arrest or severe ARDS; and the clinical indications and recommendations for ECMO/ECMO-CPR in patients with acute chemical poisoning have not yet been sufficiently studied. At the same time, as our analysis of the literature has shown, the clinical outcomes of using ECMO in patients with acute chemical poisoning are significantly better than in other categories of patients.

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