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Treating Complications of Extracorporeal Life Support in a Patient with COVID-19 (Case Report)

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Summary

We present a case of mechanical hemolysis as a complication of extracorporeal membrane oxygenation (ECMO) occurring in a COVID-19 patient as a result of pump head thrombosis. After emergency extracorporeal circuit replacement, hemoadsorption was initiated to address the negative hemolysis effects and plasma free hemoglobin rise in the setting of rapid clinical deterioration and impaired renal function. During therapy hemolysis severity reduced, the lactate dehydrogenase (LDH) levels decreased, while the P/F ratio increased two-fold. The patient was discharged from hospital on day 54 without the need for either oxygen therapy or dialysis. In the discussion section we addressed frequent issues of choosing therapy for ECMO complications.

Conclusion. The timely, properly chosen, and clinically relevant use of hemoadsorption combined with advanced high-technology therapeutic procedures can have a positive impact on the patient's outcome.

Keywords: ECMO; COVID-19; mechanical hemolysis; free hemoglobin; hemoadsorption; plasma exchange

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is one of the most high-tech accepted methods of life support in patients with refractory hypoxia who do not respond to standard ventilation techniques [1]. According to a systematic review and meta-analysis, which reviewed ECMO in COVID-19 patients and included 134 papers, ECMO procedure may be appropriate and effective in the treatment of patients with ARDS due to coronavirus infection [2]. According to the World Health Organization guidelines, the use of ECMO should be considered as a possible therapeutic option in patients with ARDS and severe COVID-19 [3].

The concept of ECMO is quite simple: it is based on a temporary maintenance of gas exchange in patients with ARDS, however, the technical implementation of this procedure presents a number of multidimensional tasks and can be associated with complications due to the mechanical effects of the system on blood components [4, 5], as well as overactivation of the complement system [6, 7]. One such complication is ECMO-associated mechanical hemolysis that develops due to damaging pressure gradients in the ECMO cannulas and circuit or thrombosis of various parts of the extracorporeal circuit. According to ELSO, hemolysis worsens the prognosis of the disease [8]. Due to impaired venous drainage into the extracorporeal circuit, excessive pressure is exerted on blood components. Damage of blood elements and increase of free hemoglobin concentration can result from this impact. Hemoglobinemia, in turn, produces a damaging effect on the kidneys and predicts the development of acute kidney injury (AKI). These processes lead to the activation of the immune response and contribute to multiple organ failure (MOF) [9]. The literature indicates that high plasma level of free hemoglobin is an independent predictor of mortality among patients undergoing ECMO [10].

Hemoadsorption has been shown to be effective in disregulated immune responses (including ones during ECMO in patients with COVID-19 [11, 12]), as well as in free hemoglobin removal [13, 14].

This paper presents a clinical observation of the efficacy of hemoadsorption in the treatment of ECMO-associated massive hemolysis in a patient with COVID-19.

Clinical Observation

Patient T., female, 49 years old, height 165 cm, weight 83 kg, body mass index (BMI) 30.4 kg/m^2,

and history of hypertension. She was on regular therapy with Telpras (telmisartan, «Laboratorios Lyconsa S.A.») and Concor (bisoprolol, «Merck KGaA»). The patient was admitted to Moscow Clinical Center for Infectious Diseases «Voronovskoe» on the 8th day from the onset of symptoms complaining of increased body temperature up to 38.5°C, malaise and dry cough. On examination the patient was found to have positive polymerase chain reaction test (PCR test) for COVID-19, severity of lung involvement according to chest computed tomography (CT) was 50% on the right side and 45% on the left side. Based on the history, physical examination and laboratory data, the clinical diagnosis of novel coronavirus infection caused by COVID-19 virus was made. The complications included bilateral multisegmental viral and bacterial pneumonia. First stage hypertension was a comorbidity. The treatment according to the standard protocol was given at the infectious diseases department according to the temporary guidelines for the treatment of novel coronavirus infection [15] which included Ilsira (levilimab, «Biocad») 324 mg, Methylprednisolone («Orion Pharma») 100 mg intravenously during an hour, then 100 mg/day, Daltep (deltaparin, «Pharmasintez») 5,000 IU 2 times/day. On day 11 of hospitalization, due to progression of respiratory failure, the patient was transferred to the ICU. On admission to the ICU, the patient complained of dyspnea and shortness of breath. Clinically, dyspnea up to 24 breaths per minute, blood oxygen saturation of 84%, moderate tachycardia up to 95 bpm at rest, NEWS score of 9 points, SOFA score of 4 points were observed. Blood pressure remained stable (123/76 mm Hg). To control hypoxemia, high-flow oxygen therapy (HFOT) was performed using the SV300 apparatus (Mindray, China) with the following parameters: flow rate 50 L/min, oxygen fraction in the breathing mixture 70%. ROX index on admission was 6.23. Prone position was used for 16 hours/day. During the next 3 days, the patient required increased respiratory support: the oxygen fraction in the inhaled mixture (FiO_2) during HFOT was increased to 90%. ROX index when transferred to noninvasive ventilation was 3.85. Noninvasive ventilation was performed with the following parameters: FiO_2 70–80%, positive end-expiratory pressure (PEEP) 8–10 cm H_2O. No effect of noninvasive ventilation was observed after 18 hours, and the patient was switched to mechanical lung ventilation (MLV) with the following initial parameters: inspiration pressure (Pinsp) 30 cm H_2O, PEEP 10 cm H_2O, FiO_2 95%. The respiratory failure deterioration was caused by increasing severity of lung damage, according to chest CT scan performed after switching to MLV, up to 75%/75% bilaterally. The P/F ratio during ventilation was 53.5 mm Hg, dynamic compliance reached 21 ml/cm H_2O, within 6 hours after transfer to MLV we used «stepwise» selection of PEEP from 10 to 15 cm H_2O, as well as prone position (without effect). Murray scale score was 3. A decision was made to transfer the patient to ECMO. Standard femoral and jugular cannulation was performed using 25 and 21 Fr cannulas (Medtronic Nextgen, Ireland). Deltastream DP3 device and Hilite 7000LT oxygenator (Medos Medizintechnik, Germany) were used for ECMO with the following baseline settings of ECMO device: flow rate 4 L/min at pump speed 6000 rpm, gas flow 4 L/min, FiO_2 100%. During the first day the patient's condition stabilized, saturation was 94%. Tracheostomy was performed 12 hours after ECMO initiation. The MLV was performed using protective parameters: Pinsp 25 cm H_2O, PEEP 10 cm H_2O, tidal volume (Vt) 272 ml (3.2 ml/kg), FiO_2 60%. Myorelaxation was used for 72 hours. After sedation was canceled, the patient was transferred to independent breathing using high-flow oxygen therapy through tracheostomy. After awakening, no pathological neurological symptoms were observed, and the Glasgow Coma Scale (GCS) score was 15.

On day 8 of ECMO impaired consciousness (9 points GCS), dark-colored urine and blood oxygen saturation reduction down to 74% were observed. CT scans of the brain and chest, as well as laboratory tests (blood chemistry) and coagulation tests were performed to diagnose possible complications of ECMO. Brain CT scan revealed no abnormalities, while a series of chest CT scans showed 90% and 95% involvement of the right and left lung, respectively, along with extensive «bacterial infiltrates» of the posterior basal areas. Laboratory tests revealed marked hemolysis with elevated LDH (7099 U/L) and indirect bilirubin (55.2 μmol/L), anemia (hemoglobin 78 g/L), increased creatinine (223 μmol/L) and urea (31.2 mmol/L). Mechanical hemolysis associated with ECMO circuit thrombosis (thrombosis of the centrifugal pump head, Fig. 1) was recognized as the cause of deterioration. The extracorporeal circuit was promptly replaced.

Hemoadsorption using CytoSorb adsorber (Cytosorbents, USA) was started immediately after ECMO circuit replacement to remove free hemoglobin and reduce the negative effects of hemolysis. The adsorber was installed in the circuit of RRT Multifiltrate apparatus (Fresenius Medical Care, Germany), operating in continuous veno-venous hemodialysis mode with a blood flow rate of 200–250 ml/min before the filter, then the entire system was connected to the lateral flow of ECMO circuit (Fig. 2).

Three consecutive hemoadsorption sessions of 24 hours each were performed. Laboratory confirmation of reduced hemolysis severity was obtained: lactate dehydrogenase (LDH) level decreased 4.3-fold (from 7099 to 1640 units/l), bilirubin down

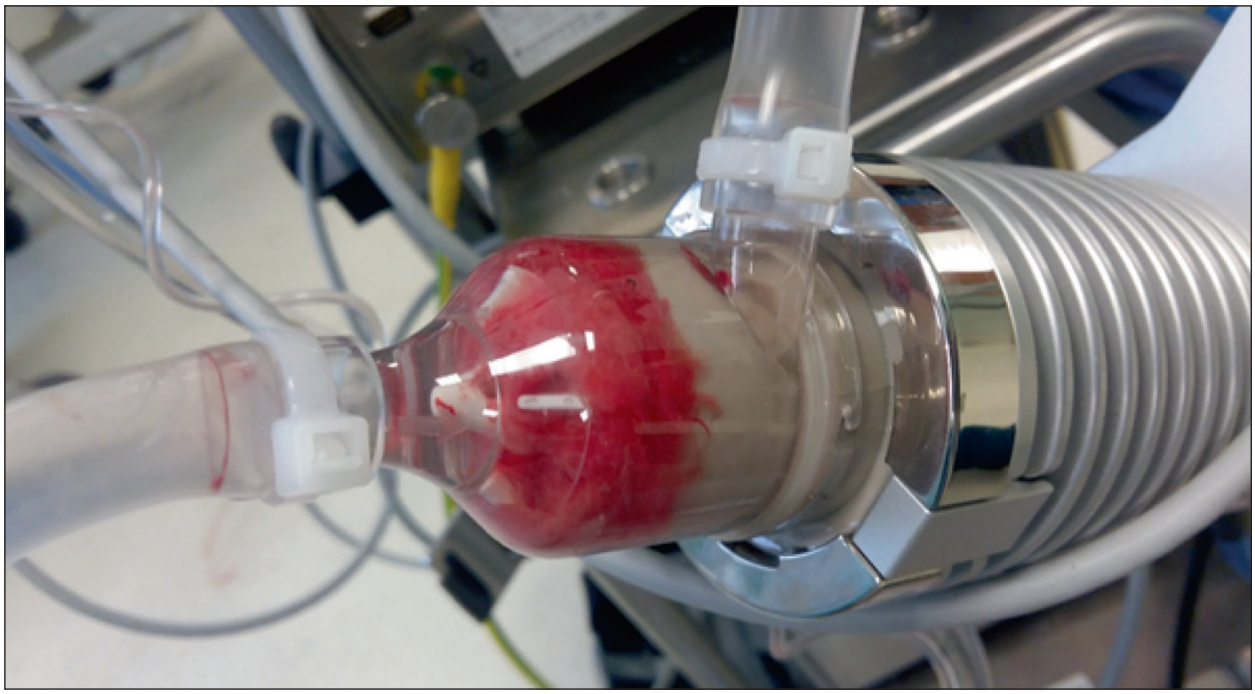

Fig. 1. Thrombosis of the centrifugal pump head of ECMO device, after circuit change.

Fig. 2. View of the extracorporeal circuit. View of centrifuged plasma before and after the first session of hemoadsorption.

to 36.7 μmol/l, and blood electrolytes returned back to normal. The P/F ratio more than doubled (from 92.1 to 200 mm Hg). The patient's clinical condition remained stable during the whole procedure (HR, BP, SpO_2, ECMO flow, blood gas parameters are given in the table below), there were no adverse effects. After ECMO flow stabilization, definition and setting of alarm limits on the renal replacement therapy (RRT) machine, the patient was put in a prone position to ensure consistency of lung ventilation.

The duration of ECMO was 19 days. Continuous veno-venous hemodialysis in the ECMO circuit was maintained for 7 days. The patient was decannulated on the 3rd day after ECMO disconnection. Urinary

Changes in clinical and laboratory parameters at different stages of treatment.

Parameter	Day									
	1	3	4	11	12	13	21	23	24	25
			ECMO start, tracheostomy	Hemoadsorption				ECMO stopped		Decannulation
				Start	Continuation					
Heart rate, bpm	62	68	89	70	68	60	59	68	76	62
Blood pressure, mm Hg	121/78	134/77	128/77	168/92	114/69	110/60	131/75	130/72	128/78	120/68
SpO_2, %	96/81	90	87	90	98	98	98	98	98	98
HFOT parameters: flow, l/min / O_2, %	50/70	50/90	50/95	60/60			50/50	40/45	60/65	60/55
NIV parameters: FiO_2, % / PEEP, cm H_2O		95%/8	95%/8							
MV parameters: FiO_2, % / PEEP, cm H_2O H_2O / P_{insp}, cm H_2O			95/10/30	50/15/15	50/8/24	50/8/24	50/8/20			
Lung involvement, CT	50/45%		75/75%	90/95%						75/80%
ECMO initiation/ ECMO circuit replacement			1	1				Stopped		
ECMO flow, l/min			3.6	4	4	3.6	3.6	3.3		
ECMO pump speed, rpm			6000	6000	6000	5600	5900	5600		
ECMO sweep gas flow, l/min			3	5	4	3	2	0		
RRT mode				CVVHD	CVVHD	CVVHD			CVVHD	
Ultrafiltration, ml/24 h				1200	600	2700			1800	
CytoSorb, h				24	24	24				
Urine output, ml/day	300	1240	2000	3400	1000	400	1100	2500	2400	1300
Laboratory values										
pH		7.293	7.278	7.338	7.365	7.454	7.283	7.244	7.268	7.152
pCO_2, mm Hg		41.6	38.1	24.1	39.8	37.9	50	51.1	44.7	49.9
pO_2, mm Hg		53.8	53.5	56.9	104	99.8	PvO_2 33	PvO_2 39	PvO_2 38.1	PvO_2 41.8
Hb, g/l		137	121	94	76	65	99	87	60	70
SpO_2, %		86.2	85.4	87.5	98.1	98.6	SvO_2 46.8	SvO_2 62.6	SvO_2 58.8	SvO_2 62.9
Lactate, mmol/l		1.8	1.2	1.5	0.9	1	1.1	0.8	1.2	0.7
HCO_3, mmol/l		19.1	17.5	19	22.4	26.8	20.9	19.5	19	15.3
Base excess, mmol/l		–5.9	–8.3	–6.8	–2.3	2.6	–2.8	–4.9	–6	–10.5
P/F ratio, mm Hg		59.7	53.5	94.8	208	200		86.7		
A-a, mm Hg		507.3	574.2	323.9	197.5	208.8		213.8		
ALT, U/l	42.9	38.40			47.5	41	38.9		21.6	
AST, U/l	30.5	29.1			93.7	25	22.7		14.2	
CRP, mg/l	41.2		98.8	21.2						
Bilirubin, mmol/l	9.6	18		55.2	36.7	17.2	18.6		11.5	12.1
Creatinine, mmol/l	60	75	60	223	190	148	173		389	175
Urea, mmol/l	6.6	6.1	5	15.3	14.3	11.6	16.5		39.9	19
LDH, U/l	1179	939	1144	7099		2510			732	
Leukocytes, $\times 10^9$	10.7	17.2	14.5	31.2	29.5	23.3	10.9	16.1	16.1	17.8
Platelets, $\times 10^9$	273	320	309	145	120	112	90	92	80	67
D-dimer, ng/ml	1485		6266	32653				7740		
Hemolysis				++++	++	—				
APTT, sec	24.4		26.3/68.3	error	error	44.5	31.6	220	error	55.1

Note. HFOT — high flow oxygen therapy; NIV — non-invasive ventilation; PEEP — positive end-expiratory pressure; P_{insp} — inspiratory pressure; CT — computed tomography; ECMO — extracorporeal membrane oxygenation; RRT — renal replacement therapy; CVVHD — continuous veno-venous hemodialysis; Hb — hemoglobin; A-a — alveolar-arterial difference in oxygen pressure; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CRP — C-reactive protein; LDH — lactate dehydrogenase; APTT — activated partial thromboplastin time.

output rate gradually increased during 7 days, however, creatinine and urea levels rose again, which required continuation of hemodialysis sessions. The patient received intermittent procedures (two hemodialysis sessions were performed). The total duration of the patient's stay in ICU was 27 days.

Renal functions were restored with fluid therapy in combination with protein-free diet (Peptoproten Nephro, Protenfarma, Russia). Full mobility returned within 2 weeks after discharge from ICU during rehabilitation in the infectious disease unit. The serial chest CT scans demonstrated reduced involvement down to 35% on both sides (Fig. 3).

The patient was discharged from the hospital on day 54 and did not require oxygen therapy or hemodialysis thereafter.

Discussion

Two extracorporeal treatments for the hemolytic complications were reported in the liter-

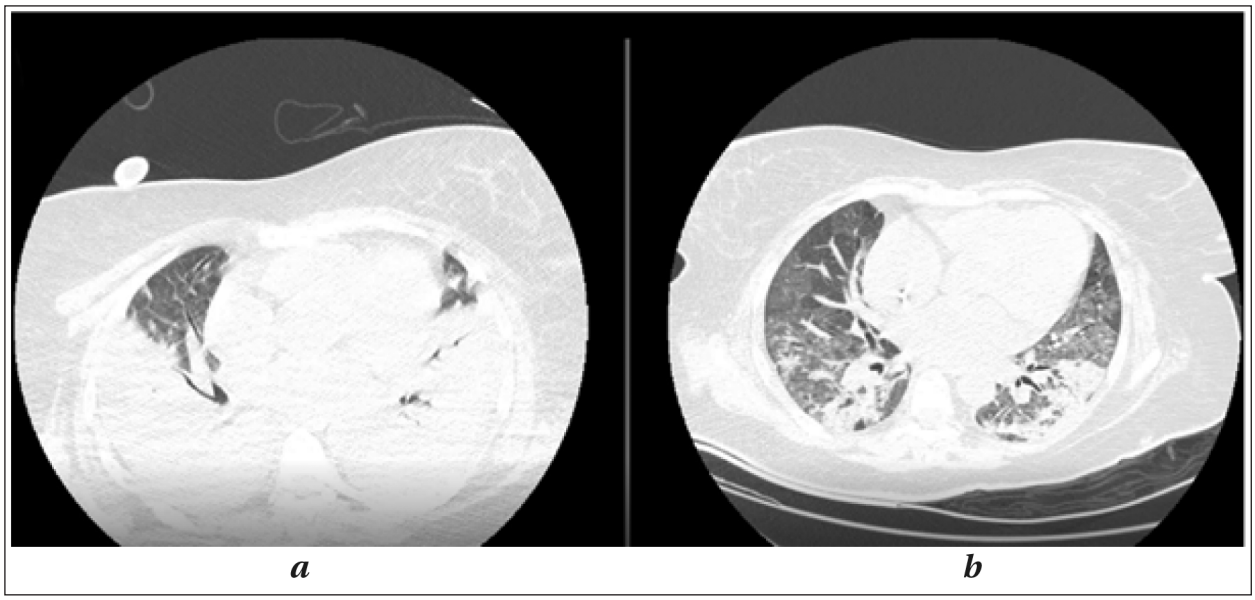

Fig. 3. The evolution of CT before (*a*) and after (*b*) the ECMO session lasting 19 days.

ature. They include therapeutic plasma exchange and hemoadsorption [16, 17]. Plasma exchange allows non-selective removal of toxic substances together with plasma. This technique is often used in autoimmune diseases therapy [18]. During the COVID-19 pandemic there were reports of the use of plasma exchange in the treatment of patients with coronavirus infection [19]. Hemoadsorption accomplishes two goals simultaneously: reduces the severity of the immune response by removing inflammatory mediators from whole blood and lowers the free hemoglobin level. Both effects occur without plasma separation [20, 21]. Publications describe the use of hemoadsorption in the treatment of hemolysis [17] and hemoglobinemia [22]. According to the results of a multicenter randomized controlled trial investigating the effectiveness of CytoSorb hemoadsorption for reducing free plasma hemoglobin during the cardiopulmonary bypass, there was a significant reduction in free hemoglobin concentration in the hemoadsorption group compared with the control one [14]. The choice of extracorporeal therapy of hemolysis in our clinical case was based on the following considerations.

During plasma exchange large volumes of blood products obtained from different donors are used, and the massive transfusion itself increases the immune burden on the recipient's body. Plasma exchange is performed once a day, on average, three sessions are required. During this time, the patient receives from 18 to 27 units of blood components from different donors. These significant volumes promote further complications, while treatment of patients without the use of donor plasma has a positive impact on clinical outcome [23]. When plasma exchange is performed along with ECMO, a frequent replacement of extracorporeal RRT circuit is required (for three sessions the circuit of plasma exchange should be connected to ECMO system three times, moreover, continuous hemodialysis needs to be restarted after the end of plasma exchange). Each circuit replacement can cause an air embolism. The human factor which could also cause serious complications cannot be neglected. The procedure is rather labor-intensive as well. Thus, we considered inappropriate the use of plasma exchange due to the higher immune burden on the patient's body and poorly studied impact of this technique on free hemoglobin concentrations in blood plasma (during 2015–2021, only 2 clinical observations were published in the available scientific literature [24, 25]).

Activation of the immune response, increased levels of damage-associated molecular patterns and elevated blood free hemoglobin as a result of the ECMO are direct indications for the use of hemoadsorption using the CytoSorb adsorber. The reduction of free hemoglobin concentration was claimed by the manufacturer of the column and confirmed in a multicenter RCT [14]. The effects of reduction of inflammatory mediators have been confirmed by an extensive body of evidence (more than 370 papers in international peer-reviewed journals) [26].

In our clinical observation, using hemoadsorption for the management of negative effects of ECMO-associated mechanical hemolysis, the reduction of hemolysis severity was confirmed by a more than 4-fold decrease in LDH, stabilization of renal function, an increase in P/F ratio by more than 2 times after the first session of hemoadsorption.

Conclusion

In this clinical observation, the use of hemoadsorption in the treatment of ECMO-associated mechanical hemolysis was safe and technically feasible, and allowed rapid and safe resolution of ECMO pump head thrombosis, as well as fast improvement of kidney function. Timely, appropriate and clinically relevant use of a complex combination therapy resulted in the patient's recovery.

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