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SHORT COMMUNICATION

First successful combination of ECMO with cytokine removal therapy in cardiogenic septic shock: A case report

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ABSTRACT

Purpose: A new hemoadsorption device intended as adjunctive treatment for patients with elevated cytokine levels in the setting of SIRS and sepsis has shown promising results. We report on the beneficial application of the device in a patient with cardiogenic septic shock receiving combined extracorporeal life support with rECMO, LVAD, and CVVH despite his highly septic condition.

Methods: A 39-year-old patient presented with fulminant ARDS and cardiogenic septic shock. A veno-arterial ECMO was implanted for circulatory support. During the course of illness, the patient developed acute renal failure in addition to his chronic renal insufficiency, making initiation of CVVH necessary. Due to a complete cardiac arrest in both ventricles, a left ventricular assist device (LVAD) in combination with right ECMO (rECMO) was implanted despite manifest septic conditions. In the post-operative course IL-6 levels and vasopressor dosages increased drastically. A CytoSorb hemoadsorption device was therefore installed in the CVVH circuit and 3 sessions were run during the following 4 days.

Results: During CytoSorb treatment, inflammatory markers IL-6, procalcitonin, and C-reactive protein decreased concomitant with significantly reduced vasopressor support. No adverse device-related side effects were documented during or after the treatment sessions.

Conclusions: This is the first clinical case report of a highly septic patient treated with the combined use of LVAD, rECMO, CVVH, and CytoSorb. The combination was practical, technically feasible, and beneficial for the patient. This combination represents a reasonable approach to improve survival in patients with multiple organ dysfunction necessitating several organ supportive techniques.

Keywords: Septic shock, Hemoadsorption, CytoSorb, LVAD, ECMO, CVVH

Background

Systemic inflammation and sepsis can be associated with acute respiratory distress syndrome (ARDS) and therefore extracorporeal membrane oxygenation (ECMO) is a frequent organ supportive technique applied in intensive care units (1). Mechanisms leading to extravascular capillary leakage of blood fluid and the subsequent development of pulmonary edema are not yet fully understood, however cytokines and their disproportionate release during systemic inflammation seem to play a crucial role in this process (2, 3). From this perspective, it would seem to be a reasonable approach to control the inflammatory response and bridge the patient until inflammation attenuates and oxygenation by the lungs has recovered. A new hemoadsorption device intended as adjunctive treatment for patients with elevated cytokine levels in the setting of SIRS, severe sepsis, and septic shock has shown promising results in septic patients (4-7). It has also proven successful in other indications associated with high cytokine levels (i.e. major cardiac surgery with the use of cardio-pulmonary bypass) (8) and therefore offers an encouraging tool for tackling this problem. In this case we report on a patient with several organ dysfunctions and the need for multiple organ supportive techniques due to fulminant ARDS and cardiogenic septic shock, respectively. The patient was successfully treated with adjuvant CytoSorb therapy. Approval of the Institutional Review Board (IRB)/Ethics Committee was not required for this study; informed consent was obtained from the patients' relatives.

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TABLE I - Markers of inflammation and organ dysfunction throughout the treatment period

	Reference	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Leucocytes (x10^3/µl)	4.5-11	11.9	12.6	15.4	15.3	11.4	12.1	12.1	12.9	14.3	13.4
Procalcitonin (ng/ml)	0-0.5	52	26	15	31	29	25	17	16	6.4	4.4
C-reactive protein (mg/dl)	0.5	18	15	21	23	19	22	18	11	11	8.6
Interleukin 6 (pg/ml)	0-15				1535	984	186	69			35
Platelets (x10^3/µl)	150-350	215	165	134	114	106	65	55	91	72	85
Fibrinogen (mg/dl)	180-350	448	535	827	562	437	617	553	421	553	513
Lactate (mmol/l)	0.6-2.2	5.4	4.3	3.6	3.3	3.0	2.6	2.1	2.3	2.2	1.6
Urea (mg/dl)	12-50	152	126	94	30	61	64	84	129	32	71
Creatinine (mg/dl)	0.7-1.3	4.0	2.7	2.0	1.2	1.9	1.7	1.9	2.7	0.78	1.3
ALT (U/l)	0-50	8	13	11	17	92	224	195	127	103	96
AST (U/l)	0-50	24	56	61	76	447	1080	631	372	231	154
Total bilirubin (mg/dl)	0.2-1	0.69	1.14	0.77	1.77	3.22	3.45	3.05	2.93	2.25	2

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Case presentation

A 39-year-old male patient with a history of dilated cardiomyopathy (left ventricular ejection fraction of 20%) from idiopathic cause was regularly scheduled for ambulant check-ups in the hospital from 2006 to 2012. Further medical history included secondary pulmonary hypertension, mitral valve insufficiency grade II to III, chronic renal failure in the state of compensated retention, hypothyroidism, and nicotine- and anabolic abuse. In 2006, a dual-chamber implantable cardioverter-defibrillator (ICD) was implanted, and the patient was planned for transplantation as from January 2007.

In early January 2013 the patient had been at our hospital for a 3-day stationary routine check. One week after his inpatient stay, the patient presented in the morning at an external hospital with dyspnea. Subsequent to a short period of primary non-invasive ventilation, the patient drastically deteriorated; he was intubated and further ventilated mechanically. Subsequent chest X-ray confirmed massive bilateral infiltrates. Within several hours, the patient developed fulminant ARDS and cardiogenic septic shock (leucocytes 18700/µl, C-reactive protein 18 mg/dl, procalcitonin 52 ng/ml) with the need for high-dose catecholamine support for hemodynamic stabilization (norepinephrine 6-8 mg/h, epinephrine 5-8 mg/h, MAP 55-60 mm/Hg).

After a telephone request from the external hospital, our team implanted a veno-arterial ECMO via the femoral artery on-site and the patient was immediately transported to our hospital. The patient further received primary therapy with Tamiflu for 4 days due to suspicion of influenza infection. On the intensive care unit the patient was ventilated in a pressure-controlled fashion and antibiotic therapy with linezolid, meropenem, moxifloxacin, voriconazol, and acyclovir was started immediately. The need for catecholamines could be reduced significantly over the following days (norepinephrine 0.5 mg/h, epinephrine 0.4 mg/h, vasopressin 0.04 units/h, MAP 65-70 mm/Hg). Bronchoalveolar-lavage two days later confirmed colonization with viridans streptococci; however PCR testing for influenza virus remained negative.

While still under treatment, the patient developed acute renal failure in addition to his chronic renal insufficiency. This included elevated creatinine and urea plasma levels (Tab. I) as well as a decline in urine excretion (data not shown). In addition, despite considerable positive fluid balancing (approximately 10 L) it was not possible to obtain negative fluid balance using diuretic drugs (etacrynic acid, furosemide i.v.). Continuous veno-venous hemofiltration (CVVH) was thus initiated, resulting in a normalization of creatinine and urea plasma levels (Tab. I) over the following days. However, due to a global cardiac akinesia and high risk of intracardial thrombosis, we decided to implant a left ventricular assist device (LVAD; Heartware, Framingham, MA, USA) in combination with a right ECMO (rECMO, Centrimag; Thoratec, Pleasanton, CA, USA) in exchange for the veno-arterial ECMO to obtain right- and left-ventricular assistance and hemodynamic stabilization. For this combined procedure, a sternotomy was performed. The rECMO was connected between the vena cava (femoral venous cannula inserted to the level of the right atrium) and pulmonary artery using an end-to-side anastomosis with an 8 millimeter hemashield prosthesis into which a standard cannula was inserted. The LVAD Heartware was implanted between the left apex and the aorta ascendens.

Importantly, the operation was carried out despite full-blown sepsis. The post-operative clinical condition of the patient further deteriorated over the next few hours, as expected, creating the need for high-dosage vasopressor therapy (norepinephrine 2 mg/h, epinephrine 1 mg/h, vasopressin 0.32 units/h). The worsened clinical condition in combination with progressing leucocytosis (15300/µl), a highly elevated interleukin-6 plasma concentration (1535 pg/ml) and excess

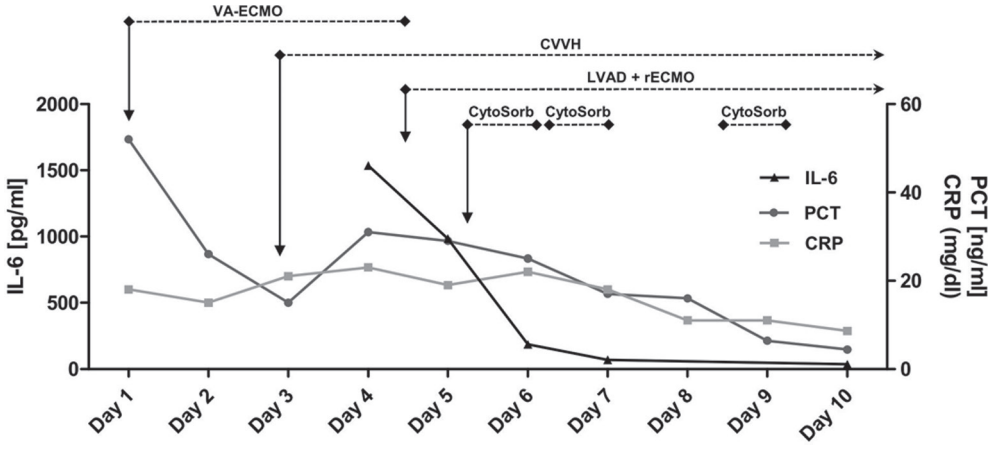

Fig. 1 - Treatment regimen and course of IL-6, procalcitonin, and C-reactive protein before, during, and after treatment with CytoSorb. VA = veno-arterial; ECMO = extracorporeal membrane oxygenation; CVVH = continuous veno-venous hemofiltration; LVAD = left ventricular assist device; rECMO = ECMO from vena cava to pulmonary artery.

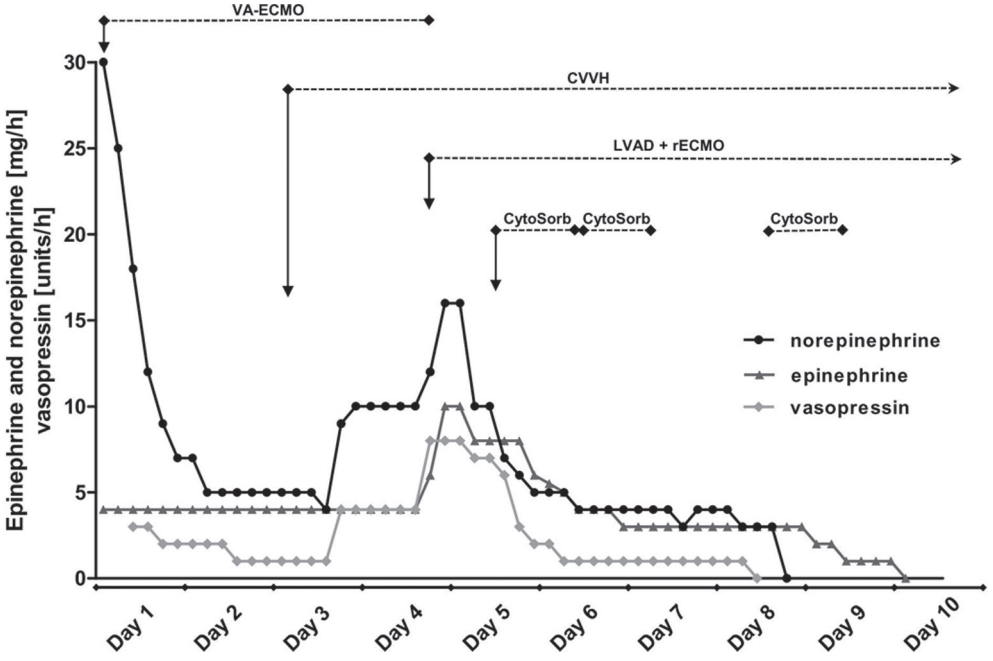

Fig. 2 - Treatment regimen and need for vasopressors before, during and after treatment with CytoSorb. VA = veno-arterial; ECMO = extracorporeal membrane oxygenation; CVVH = continuous veno-venous hemofiltration; LVAD = left ventricular assist device; rECMO = ECMO from vena cava to pulmonary artery.

levels of lactate (3.3 mmol/l) pointed towards ongoing, high-grade sepsis.

As a last resort decision, a CytoSorb hemoadsorption device (CytoSorbents Europe, Berlin, Germany) was installed into the CVVH circuit (AK200; Gambro, Lund, Sweden). The CytoSorb adsorber was connected in series, placed before the hemofilter cartridge, and was connected to the patient via a Sheldon catheter in the internal jugular vein. Sessions were run on the first day as well as on day 2 and 4 after the operation over periods of 18 to 21 h each. Blood flow rates were between 155 ml/min and 240 ml/min; anticoagulation was achieved using heparin, targeting a partial thromboplastin time (PTT) of 60 to 80, monitored every 4 h. Besides that, ATIII, fibrinogen, and platelet count were determined every 8 h and substituted as necessary. Importantly, a direct installation of CytoSorb into the ECMO circuit bears the risk of air aspiration and leakage and is therefore strictly contraindicated.

During the entire treatment period (4 days in total), the patient received linezolid, meropenem, moxifloxacin, voriconazol, and acyclovir as boluses with no adaptation of the dose at any time. With start of the CytoSorb therapy in combination with ECMO, inflammatory markers IL-6, procalcitonin, and CRP markedly decreased during treatment and continued to decrease further in the following days (Fig. 1). Also, we were able to reduce vasopressors significantly and stop them during (norepinephrine and vasopressin) and shortly after (epinephrine) the last treatment (Fig. 2). Importantly, no negative effects on platelet count were observed and doses of antibiotics did not have to be adjusted at any time. The rECMO was explanted 19 days and ventilation was stopped 27 days after cessation of treatment. For regeneration of the kidney, the patient received CVVH for another 21 days and was discharged from ICU at 38 days and from the hospital 76 days after the last CytoSorb session with the LVAD Heartware system. The patient is still listed for transplantation.

Conclusions

This is the first clinical case report in a patient treated with LVAD, rECMO, CVVH, and CytoSorb in a combined fashion. It turned out that this combination was practical, technically feasible and highly beneficial for the patient. No adverse or any device-related side effects were documented during or after the treatment sessions. Due to the certainly complex medical treatment of this patient, including multi-support both mechanically and pharmacologically, it is ambitious to conclude that CytoSorb was the keystone of the successful treatment. However, because the patient's condition deteriorated drastically after the major surgical procedure, with signs of extremely severe septic shock and highest levels of vasopressor support, we decided to use CytoSorb as the last resort procedure in this situation. After commencement of CytoSorb treatment, the patient's inflammatory status improved and vasopressor support could be reduced and tapered out. This is in line with other case reports and clinical studies reporting similar effects on inflammation and clinical outcomes (4-8).

Of note, several other positive effects of hemoadsorption have been described previously. Peng and colleagues showed in an animal model of abdominal sepsis (fecal peritonitis) that CytoSorb was able not only to effectively reduce circulating cytokine levels, but also to have a positive effect on hemodynamics (improved MAP) and short-term survival (9). The same group found that hemoadsorption using CytoSorb could decrease the *de novo* synthesis of inflammatory mediators and even stop and prevent cytokine- and mediator-induced tissue injury (10).

Moreover, there is evidence from animal studies that hemoadsorption might have a direct effect on the cellular immune response by modulation of chemokine gradients and redirection of leukocyte trafficking to the site of infection (11, 12).

Taken together, CytoSorb could be simply used in combination with ECMO, resulting in considerable benefits for the patient, thus representing a reasonable approach to improve survival in patients with several organ dysfunctions and the need for multiple organ supportive techniques.

Abbreviations

ARDS	Acute respiratory distress syndrome
CVVH	Continuous veno-venous hemofiltration
ECMO	Extracorporeal membrane oxygenation
rECMO	ECMO from vena cava to pulmonary artery
ICD	Implantable cardioverter-defibrillator
LVAD	Left ventricular assist device
VA	Veno-arterial

Disclosures

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Conflict of interest: None of the authors have any conflicts of interest associated with this report.

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