




MAIN TEXT

Extracorporeal carbon dioxide removal with the Advanced Organ Support system in critically ill COVID-19 patients

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Abstract

Disturbed oxygenation is foremost the leading clinical presentation in COVID-19 patients. However, a small proportion also develop carbon dioxide removal problems. The Advanced Organ Support (ADVOS) therapy (ADVITOS GmbH, Munich, Germany) uses a less invasive approach by combining extracorporeal CO₂-removal and multiple organ support for the liver and the kidneys in a single hemodialysis device. The aim of our study is to evaluate the ADVOS system as treatment option in COVID-19 patients with multi-organ failure and carbon dioxide removal problems. COVID-19 patients suffering from severe respiratory insufficiency, receiving at least two treatments with the ADVOS multi system (ADVITOS GmbH, Munich, Germany), were eligible for study inclusion. Briefly, these included patients with acute kidney injury (AKI) according to KDIGO guidelines, and moderate or severe ARDS according to the Berlin definition, who were on invasive mechanical ventilation for more than 72 hours. In total, nine COVID-19 patients (137 ADVOS treatment sessions with a median of 10 treatments per patient) with moderate to severe ARDS and carbon dioxide removal problems were analyzed. During the ADVOS treatments, a rapid correction of acid-base balance and a continuous CO₂ removal could be observed. We observed a median continuous CO₂ removal of 49.2 mL/min (IQR: 26.9–72.3 mL/min) with some treatments achieving up to 160 mL/min. The CO₂ removal significantly correlated with blood flow (Pearson 0.421; $P < .001$), PaCO₂ (0.341, $P < .001$) and HCO₃⁻ levels (0.568, $P < .001$) at the start of the treatment. The continuous treatment led to a significant reduction in PaCO₂ from baseline to the last ADVOS treatment. In conclusion, it was feasible to remove CO₂ using the ADVOS system in our cohort of COVID-19 patients with acute respiratory distress syndrome and multiorgan failure. This efficient removal of CO₂ was achieved at blood flows up to 300 mL/min using a conventional hemodialysis catheter and without a membrane lung or a gas phase.

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**KEYWORDS**ADVOS, ARDS, COVID-19, extracorporeal CO₂ removal (ECCO₂R), multiple organ support

1 | INTRODUCTION

Since the outbreak of the COVID-19 pandemic, most patients present with either none or mild symptoms. However, up to 15% of COVID-19 patients need hospitalization and nearly 5% need intensive care unit (ICU) support including mechanical ventilation and, in few cases, further extracorporeal organ support.^{1,2} Based on a hyperactive “cytokine storm”, an uncontrolled systemic inflammatory state leads to an acute respiratory failure and in 14% of all cases, acute respiratory distress syndrome (ARDS) with an impairment of gas exchange for both oxygen and carbon dioxide (CO₂).³⁻⁶ Disturbed oxygenation is foremost the leading clinical presentation in COVID-19 patients. However, a small proportion also develop carbon dioxide removal problems.⁷ In order to avoid ventilator induced lung injury (VILI), lung-protective ventilation with low tidal volume and low driving pressure using extracorporeal carbon dioxide removal systems are emerging in a potential respiratory support strategy.⁸⁻¹⁰

ECCO₂R uses medium to low blood flows of up to 500 mL/h.¹¹ In contrast to ECMO, ECCO₂R is less invasive and requires lower blood flows. High invasiveness and high blood flows may be a limiting factor particularly in elderly patients and those with multiple comorbidities.^{12,13} Systems operating at lower blood flows such as ECCO₂R, working either alone or in combination with renal replacement therapy (RRT) have already shown feasibility in COVID-19 patients with ARDS.¹⁴ Nevertheless, this approach is not exempt of side effects, as shown in larger studies.¹⁵⁻¹⁷ However, the possibility of ECCO₂R improving the outcome of affected COVID-19 patients has yet to be shown in larger studies.

The Advanced Organ Support (ADVOS) therapy (ADVITOS GmbH, Munich, Germany) uses a less invasive approach by combining extracorporeal CO₂-removal and multiple organ support for the liver and the kidneys in a single hemodialysis device. The low invasiveness of this system combined with the possibility of fluid-based CO₂ removal and acid-base balance correction may be a promising approach for COVID-19-associated ARDS patients with multiple comorbidities.¹⁸⁻²¹

The aim of our study is to evaluate the ADVOS system as treatment option in COVID-19 patients with multi-organ failure and carbon dioxide removal problems.

2 | METHODS

2.1 | Study design, settings and patients

This observational cohort study was conducted at a tertiary care ICU (department of internal medicine) of the University Hospital of Technical University of Munich, Germany. Patients (18 years of age or older) with confirmed severe COVID-19 pneumonia (clinical signs, typical laboratory constellation, PCR test for SARS-CoV-2 positive and chest computed tomography (CT) scan with typical signs) who were admitted to the ICU due to acute respiratory failure were eligible for study inclusion. The study was approved by the institutional review board of the Technical University of Munich, Germany (178/20S). Written informed consent was obtained by the patient or their legal representatives.

COVID-19 patients suffering from severe respiratory insufficiency, receiving at least two treatments with the ADVOS multi system (ADVITOS GmbH, Munich, Germany), were eligible for study inclusion. Briefly, these included patients with acute kidney injury (AKI) according to KDIGO guidelines,²² and moderate or severe ARDS according to the Berlin definition,²³ who were on invasive mechanical ventilation for more than 72 hours. Patients without informed consent, pregnant patients, as well as patients under 18 years of age were excluded.

2.2 | Intervention

The ADVOS multi system is an albumin hemodialysis system which operates with conventional dialysis catheters with blood flows between 100 and 400 mL/min. The system has been described and characterized in previous publications.¹⁸⁻²⁰ Briefly, three circuits (the extracorporeal circuit, the dialysate circuit and the ADVOS multi circuit) allow water-soluble and protein-bound toxins removal and acid-base balance correction (Figure 1). In the extracorporeal circuit, toxins diffuse through two semi-permeable high-flux membranes (ELISIO-19H, Nipro, Osaka, Japan) into the dialysate circuit. For an enhanced protein-bound toxins removal, albumin is added into the dialysate, which is continuously regenerated by pH and temperature changes in the ADVOS multi circuit. This modifiable dialysate additionally enables an acid-base balance correction and a fluid-based CO₂ removal through

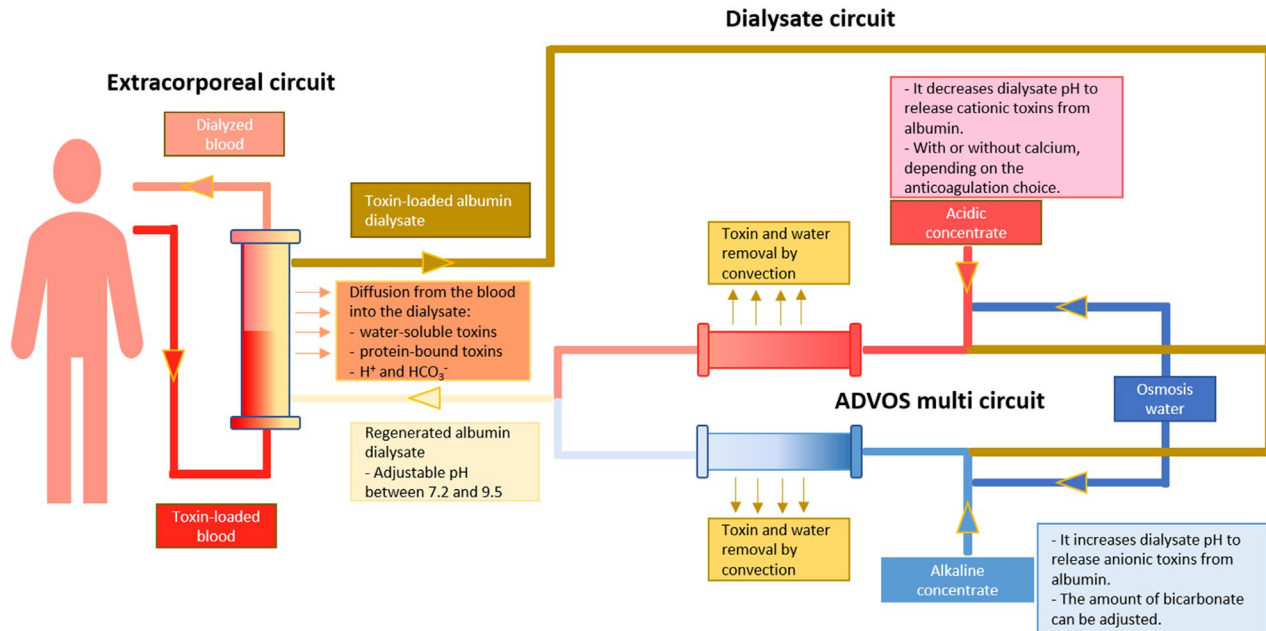


FIGURE 1 Schematic view of the ADVOS multi device [Color figure can be viewed at wileyonlinelibrary.com]

the correction and, if needed, removal of H^+ and HCO_3^- , as described in detail in the discussion.²⁰ Citrate anticoagulation was used in all patients during the treatment.

2.3 | Data documentation and follow-up

Routinely assessed laboratory parameters including creatine, blood urea nitrogen (BUN), C-reactive protein (CRP), procalcitonin, bilirubin, calcium, albumin, INR, activated thromboplastin time, leucocytes, platelets, hemoglobin, and blood gas analysis were documented. Additionally, ventilation parameters including tidal volume, minute ventilation, respiratory rate, positive expiratory pressure, peak pressure, fraction of inspired oxygen (FiO_2), positive inspiratory pressure, and oxygen saturation were assessed. Finally, clinical data on pre-existing illnesses, catecholamine doses, and ADVOS treatment parameters were documented using a clinical information system. For the analysis, available parameters immediately before and immediately after each ADVOS session were analyzed. To quantify the removal capacity blood gas analysis at the inlet and the outlet of the dialyzers were performed. The following equation was used for the calculation of CO_2 removal in mL/min ^{20,24}:

$$V_{CO_2} = (\Delta HCO_3^- + \Delta pCO_2 * K_s) * Q_b * V_m$$

In this equation, ΔHCO_3^- and ΔpCO_2 represent the difference between the inlet and the outlet of the dialyzer for HCO_3^- and pCO_2 in $mmol/L$ and $mm\ Hg$, respectively; K_s

is the solubility constant for CO_2 in blood ($0.03\ mmol/L/mm\ Hg$); Q_b is the corresponding blood flow in l/min at the time of the blood analysis; and V_m is the molar volume of CO_2 at STP ($22.4\ mL/mmol$).

Patients were followed up until hospital discharge or until death.

2.4 | Statistical analysis

Variables were reported as median and 25%-75% interquartile range (IQR), if not stated otherwise. The Student t test for paired samples was used to compare values before and after ADVOS sessions and individual treatments. For correlations assessment, Pearson's coefficient was used. The median differences were calculated subtracting the post-therapy from pre-therapy values for the first treatment in each patient and for the 137 treatments independently of the patient. Similarly, pre-therapy values were compared with values after the last ADVOS session for each of the patients. A two-tailed p value lower than 0.05 was considered to indicate statistical significance. Data were analyzed with IBM SPSS 27.0 for Windows.

3 | RESULTS

3.1 | Patients' characteristics

In total, nine COVID-19 patients with moderate to severe ARDS and carbon dioxide removal problems were



TABLE 1 Base line characteristics

Characteristics	Categories	All (n = 9)
Age	Median (IQR 25%-75%)	60 (53-77)
Sex		
Female	Number (%)	3 (33)
Male	Number (%)	6 (67)
Weight (kg)	Median (IQR 25%-75%)	80 (77.50-94.00)
Height (cm)	Median (IQR 25%-75%)	174 (166-182)
BMI	Median (IQR 25%-75%)	29.0 (23.4-32.4)
Overweight (BMI ≥ 25)	n (%)	1 (11)
Obesity (BMI ≥ 30)	n (%)	4 (44)
Scores		
WHO COVID-19 scale	Median (IQR 25%-75%)	8 (7-8)
SOFA ^a	Median (IQR 25%-75%)	9 (9-11)
APACHE II	Median (IQR 25%-75%)	21 (18-24)
Comorbidities		
Diabetes	n (%)	4 (44)
Cardiac disease	n (%)	4 (44)
Coronary artery disease	n (%)	1 (11)
Hypertension	n (%)	6 (67)
Neoplasia	n (%)	4 (44)
COPD	n (%)	1 (11)
Asthma	n (%)	1 (11)
Liver cirrhosis	n (%)	1 (11)
Ascites	n (%)	0 (0)
Hepatic encephalopathy	n (%)	0 (0)
Chronic kidney disease	n (%)	4 (44)
Prior dialysis performed (>2x/ week)	n (%)	4 (44)
Pancreatitis	n (%)	1 (11)

^aSOFA GCS subscore: a Glasgow Coma Score of 15 was assumed due to the impossibility to assess it correctly in sedated patients.

analyzed. Patients' characteristics and individual case reports at baseline (immediately before the first ADVOS session) are presented in Table 1 and Table S1, respectively.

3.2 | ADVOS treatments

In total, 137 ADVOS treatment sessions with a median of 10 treatments per patient (IQR: 8-20 treatments) and a median duration of 22 hours (IQR: 15-24 h) were performed (Table 2). A median blood flow of 300 mL/min (IQR: 250-300 mL/min) and a median dialysate pH setting of 8.6 (IQR: 8.4-8.8) was employed. Regional citrate anticoagulation was applied in all sessions, either alone (8%) or in combination with unfractionated heparin (92%). Details on ADVOS settings and anticoagulation rates can be found in Table 2.

3.3 | Rapid correction of acid-base balance and continuous CO₂ removal

During the ADVOS treatments, a rapid correction of acid-base balance and a continuous CO₂ removal could be observed. A significant removal of water-soluble substances (ie, creatinine 1.5 vs. 0.8 mg/dL, $P = .01$ and BUN 30 vs. 11 mg/dL, $P = .003$), a significant improvement in blood pH (7.26 vs. 7.41, $P = .003$), serum bicarbonate and base excess were achieved after the first ADVOS treatment (Table 3). Changes for blood pH are shown in Figure 2A.

We observed a median continuous CO₂ removal of 49.2 mL/min (IQR: 26.9-72.3 mL/min) with some treatments achieving up to 160 mL/min (Figure 2C). The CO₂ removal significantly correlated with blood flow (Pearson 0.421; $P < .001$), PaCO₂ (0.341, $P < .001$) and HCO₃⁻ levels

TABLE 2 ADVOS treatment settings, anticoagulation regimens, and treatment abortions

Treatment setting	Categories	All (n = 137) beginning of individual ADVOS treatment
ADVOS treatments		
Total number of treatments	Number	137
ADVOS treatments per patient	Median (IQR 25%-75%)	10 (8-20)
Treatment duration (h)	Median (IQR 25%-75%)	22 (15-24)
ADVOS settings		
Blood flow max. (mL/min)	Median (IQR 25%-75%)	300 (250-300)
Dialysate pH	Median (IQR 25%-75%)	8.8 (8.5-9.0)
Concentrate flow (mL/min)	Median (IQR 25%-75%)	320 (160-320)
Ultrafiltration rate (mL/h)	Median (IQR 25%-75%)	100 (20-170)
Anticoagulation		
No anticoagulation	n (%)	0 (0)
Citrate (alone)	n (%)	11 (8)
Citrate rate (mL/h)	Median (IQR 25%-75%)	353 (228-490)
Calcium rate (mL)	Median (IQR 25%-75%)	18 (12-20)
Ionized calcium pre-dialyzer (mmol/L)	Median (IQR 25%-75%)	1.20 (1.12-1.29)
Ionized calcium post-dialyzer (mmol/L)	Median (IQR 25%-75%)	0.27 (0.26-0.31)
UFH (alone)	n (%)	0 (0)
Citrate and UFH	n (%)	126 (92)
Citrate rate (mL/h)	Median (IQR 25%-75%)	446 (268-558)
Calcium rate (mL/h)	Median (IQR 25%-75%)	19 (13-21)
Ionized calcium pre-dialyzer (mmol/L)	Median (IQR 25%-75%)	1.15 (1.07-1.22)
Ionized calcium post-dialyzer (mmol/L)	Median (IQR 25%-75%)	0.31 (0.27-0.34)
Heparin dose (IU/h)	Median (IQR 25%-75%)	800 (400-1300)
Number of treatments aborted		
Clotting	N (%)	8 (6)
Malfunctioning	N (%)	15 (11)
n.d.	N (%)	1 (1)
Duration of aborted treatments (h)	Median (IQR 25%-75%)	14 (11-18)

(0.568, $P < .001$) at the start of the treatment. The continuous treatment led to a significant reduction in PaCO₂ from baseline to the last ADVOS treatment (Table 3, Figure 2B). Differences of pCO₂ between the inlet and the outlet of the dialyzer are shown in Table 4. The respiratory acidosis could be shifted towards physiological values via the removal of CO₂. No significant changes were observed in ventilation parameters. The in-hospital mortality in our cohort was 55% and the median ICU-length of stay was 24 days (IQR: 18-50 days).

4 | DISCUSSION

The results of our study demonstrate the feasibility of the ADVOS multi albumin hemodialysis device for

continuous CO₂ removal in COVID-19 patients with acute respiratory distress syndrome and carbon dioxide removal problems. With the fluid-based removal method a continuous median elimination of 49 mL/min CO₂ could be achieved using blood flows of 300 mL/min in addition to the organ support (RRT) function. Various authors have shown that a combination of ECCO₂R devices with a CRRT circuit is feasible.^{16,25} In addition, this combined approach allows the application of a multiple organ support strategy with one single device with a low flow extracorporeal circuit. Currently, only results of a small cohort with four COVID-19 and moderate ARDS patients using a combined extracorporeal strategy had been reported.¹⁴

Extracorporeal CO₂ removal has gained attention in recent years for several reasons. In vivo experiments by



TABLE 3 Comparison of main laboratory, hemodynamic, blood gas, and ventilator parameters between baseline values immediately before the first ADVOS treatment and values after the first and the last ADVOS treatments for the nine patients

	Baseline (<i>n</i> = 9)			After first treatment (<i>n</i> = 9)			After last treatment (<i>n</i> = 9)		
	Median (IQR 25%-75%)	Mean difference vs. baseline	<i>P</i> -value	Median (IQR 25%-75%)	Mean difference vs. baseline	<i>P</i> -value	Median (IQR 25%-75%)	Mean difference vs. baseline	<i>P</i> -value
Laboratory parameters									
Creatinine (mg/dL)	1.50 (0.85-3.25)	-1.00	.010	0.80 (0.45-1.35)	-1.00	.010	0.60 (0.45-1.00)	-1.09	.009
BUN (mg/dL)	30 (25-56)	-29.22	.003	11 (6-23)	-29.22	.003	17 (9-33)	-23.33	.080
Total bilirubin (mg/dL)	0.50 (0.30-1.25)	0.26	.286	0.50 (0.35-1.85)	0.26	.286	8.70 (0.35-15.40)	6.92	.023
Calcium (mmol/L)	2.02 (1.90-2.22)	0.34	.20	2.27 (2.12-2.73)	0.34	.20	2.52 (2.01-2.75)	0.37	.04
Albumin (g/dL)	2.6 (2.3-3.0)	-0.37	.072	2.4 (2.1-3.1)	-0.37	.072	2.5 (2.4-3.2)	-0.06	.771
CRP (mg/dL)	17.1 (11.5-23.4)	1.60	.638	15.5 (9.1-32.4)	1.60	.638	11.4 (5.9-21.3)	-3.80	.488
Procalcitonin (ng/mL)	0.80 (0.30-4.65)	-0.60	.714	3.6 (0.65-8.95)	-0.60	.714	1.10 (0.45-8.40)	8.86	.264
INR	1.00 (0.90-1.05)	0.022	.447	1.00 (0.95-1.10)	0.022	.447	1.10 (0.95-4.20)	1.19	.084
aPTT (s)	42 (38-58)	2.11	.597	51 (37-63)	2.11	.597	58 (35-90)	12.56	.334
Leukocytes (10 ⁹ /L)	6.78 (5.60-12.50)	0.50	.562	7.33 (5.79-11.26)	0.50	.562	14.30 (7.65-15.54)	3.97	.017
Hemoglobin	10.2 (9.3-12.9)	-1.54	.009	8.9 (8.3-10.3)	-1.54	.009	9.1 (8.6-9.6)	-1.61	.090
Platelets (10 ⁹ /L)	166 (113-270)	-51.88	.96	135 (79-187)	-51.88	.96	61 (28-174)	-97.25	.034
Hemodynamic parameters									
Mean arterial pressure (mm Hg)	78 (75-82)	-2.29	.62	77 (77-78)	-2.29	.62	69 (68-69)	-7.5	.205
Noradrenalin dose (µg/kg/min)	0.229 (0.117-0.315)	-0.108	.116	0.104 (0.232-0.138)	-0.108	.116	0.250 (0.026-0.609)	0.95	.300
Blood gas analysis parameters									
pH	7.26 (7.16-7.34)	0.14	.003	7.41 (7.31-7.46)	0.14	.003	7.29 (7.20-7.41)	0.05	.219
pCO ₂ (mm Hg)	66.2 (53.5-71.1)	-5.94	.262	52.2 (45.3-68.2)	-5.94	.262	47.8 (44.2-58.6)	-13.31	.017
pO ₂ (mm Hg)	82.2 (70.0-96.4)	3.08	.770	81.7 (77.4-96.2)	3.08	.770	78.7 (65.7-83.5)	-9.57	.335
HCO ₃ (mmol/L)	25.2 (20.4-31.9)	7.31	.005	30.1 (27.6-42)	7.31	.005	21.7 (19.7-32.7)	-0.83	.712
Base excess (mmol/L)	-4.1 (-7.1- -5.4)	9.06	.002	5.2 (1.8-14.9)	9.06	.002	-5.0 (-7.9-8.0)	0.46	.846
Sodium (mmol/L)	139 (136-142)	1.78	.303	140 (137-143)	1.78	.303	141 (137-145)	1.33	.614
Potassium (mmol/L)	4.4 (4.0-5.5)	-0.54	.041	4.2 (3.8-4.2)	-0.54	.041	4.6 (3.8-5.2)	0	1.00
Cl ⁻ (mmol/L)	108 (102-111)	-4.22	.020	103 (101-106)	-4.22	.020	101 (99-107)	-4.78	.066
Ca ²⁺ (mmol/L)	1.10 (1.02-1.18)	-0.24	.023	1.31 (1.22-1.51)	-0.24	.023	1.01 (0.84-1.29)	-0.06	.542
Anion gap (mmol/L)	11.2 (3.6-13.9)	-1.76	.277	7.7 (4.0-11.2)	-1.76	.277	12.2 (6.9-24.4)	6.96	.049
Lactate (mmol/L)	1.30 (0.95-1.85)	0.86	.126	1.60 (1.25-3.20)	0.86	.126	2.5 (0.9-15.7)	6.30	.042

(Continues)

TABLE 3 (Continued)

	Baseline (n = 9)		After first treatment (n = 9)		After last treatment (n = 9)	
	Median (IQR 25%-75%)	Mean difference vs. baseline	Median (IQR 25%-75%)	Mean difference vs. baseline	Median (IQR 25%-75%)	Mean difference vs. baseline
Ventilation parameters						
V_T	461 (434-505)	-24.38	425 (350-557)		508 (394-610)	23.14
V_T /kg PBW	6.8 (6.2-8.1)	-0.41	6.3 (5.8-7.3)		7.2 (4.9-9.0)	0.41
Minute ventilation	12.6 (10.7-14.4)	-1.20	10.5 (9.4-12.9)		9.7 (7.9-11.9)	-3.99
Respiratory rate	26 (26-27)	-0.38	27 (25-28)		22 (14-28)	-5.14
PEEP	14 (11-17)	-0.33	14 (10-16)		12 (10-16)	-0.71
Peak pressure	33 (29-36)	1.00	34 (30-37)		35 (23-41)	-0.57
FiO ₂	0.85 (0.48-0.98)	-0.005	0.70 (0.58-0.90)		0.40 (0.35-0.95)	-0.09
Positive inspiratory pressure	21 (17-27)	0.75	22 (20-29)		22 (16-30)	-1.67
Driving pressure	20 (14-22)	1.33	20 (16-23)		22 (15-25)	0.14
PaO ₂ /FiO ₂	134 (87-160)	-2.11	127 (98-157)		205 (83-224)	46.43
SPO ₂ /FiO ₂	109 (96-192)	-6.67	130 (105-168)		234 (108-292)	68.33

The bold values are the significant *P* values.

Gattinoni et al have provided a physiological rationale for extracorporeal CO₂ removal, demonstrating that it is an effective way to mobilize CO₂ stores in the body and that the relative change of PaCO₂ is related to the amount of CO₂ stores mobilized.²⁶ These findings are consistent with previous in vitro data with the ADVOS system removing up to 25% of the body's normal CO₂ (assuming the amount of CO₂ produced by a healthy adult human is 210 mL/min).^{20,27}

Beside these in vitro experiments it is well known that severe hypercapnia affects the function of extrapulmonary organs including the brain and the cardiovascular system in a negative manner.²⁸ Moreover, hypercapnic acidosis is described to increase pulmonary vasoconstriction and furthermore increases the right ventricular afterload.²⁹ Beyond these side-effects of hypercapnia the main approach to decrease elevated carbon dioxide levels is to avoid ventilator induced lung injury as a consequence of an inhomogeneous lung overdistension.³⁰

Pilot studies suggest that CO₂ removal at lower blood flows than ECMO is feasible to facilitate an ultraprotective ventilation in a less invasive way and limit ventilator-induced lung injury in ARDS patients.^{15,16} However, effects of ECCO₂R are limited and a combination with other devices is needed to provide multiple organ support in a substantial proportion of critically ill patients.

In contrast to other ECCO₂R devices using a pressure gradient between blood and a gas phase, the ADVOS system removes CO₂ in an indirect manner, by diffusion of H⁺ and HCO₃⁻ according to a concentration gradient between blood and an adaptable dialysate. The dialysate is constituted online by mixing an acidic concentrate (mainly, HCl and other electrolytes), an alkaline concentrate (mainly, NaOH and, optionally, bicarbonate), osmosis water and albumin (200 mL of a 20% solution for a 24-hour session). By recirculation and regeneration of the dialysate, water-soluble and protein-bound toxins, or excess H⁺ and HCO₃⁻ can be removed.^{18,20} Using HCL and NaOH concentrates (instead of other conventional e.g., acetate concentrates) enables changes of pH and temperature in the internal hydraulics of the ADVOS system triggering the release of such toxins. These changes permit an adjustment of the dialysate pH between 7.4 and 9.5, which favors a concentration gradient-driven diffusion of H⁺ from blood (in case of acidosis) into the dialysate. Similarly, the bicarbonate content of the dialysate can be adapted depending on the amount of carbonate contained in the alkaline concentrate, removing HCO₃⁻ from blood during respiratory acidosis or increasing blood levels in case of metabolic acidosis. This basic chemical principle, which is also physiologically employed by the kidney for acidosis compensation,^{31,32} is the proposed mechanism for CO₂ removal and acid-base balance correction during ADVOS treatments, as described in detail elsewhere.^{20,33}



FIGURE 2 Rapid correction of acid-base balance and continuous CO₂ removal during ADVOS treatments. A, Arterial blood pH change during the first ADVOS session in each patient; B, PaCO₂ change from baseline to after last ADVOS session in each patient; C, Frequency of CO₂ removal in ADVOS treatments [Color figure can be viewed at wileyonlinelibrary.com]

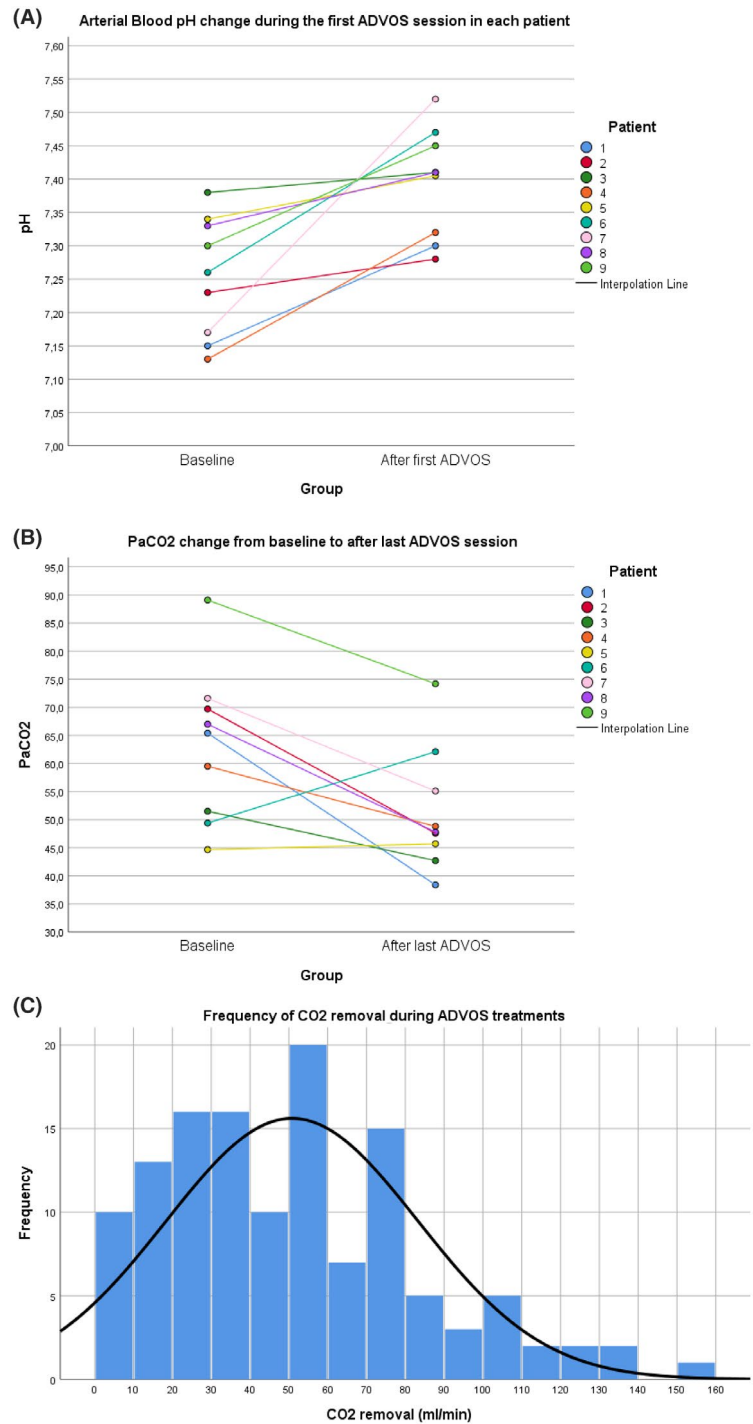


TABLE 4 Changes in pH, pCO₂, and HCO₃⁻ between the inlet and the outlet of the dialyzer during ADVOS treatments. Overall complete data sets from 128 treatments were available

	Pre-dialyzer (n = 128)	Post-dialyzer (n = 128)		
	Median (IQR 25%-75%)	Median (IQR 25%-75%)	Mean difference	P-value
pH	7.35 (7.29-7.42)	7.59 (7.46-7.69)	0.20	.000
pCO ₂ (mm Hg)	63.1 (53.6-72.8)	28.1 (23.0-38.1)	-31.78	.000
HCO ₃ (mmol/L)	34.9 (30.3-38.2)	27.7 (23.7-32.3)	-7.25	.000

The bold values are the significant *P* values.



The efficiency of the process was correlated with three major aspects, which had been underlined in previous *in vitro* analyses²⁰: Firstly, the starting CO₂ levels (high levels of CO₂ resulted in a higher removal). Secondly, the dialysate pH setting (the CO₂ removal is more effective with a dialysate pH >8.5) and thirdly, the blood flow (the higher the blood flow the higher the removal).

In contrast to the CO₂ removal devices combined with a renal replacement therapy device, ADVOS provides a combined support for kidney, liver, lung and acid-base balance correction in a single device using a conventional dialysis catheter. In the device patients' blood interacts with the albumin dialysate while a direct contact to a gas phase is avoided; thus, reducing the probability of adverse events. Moreover, our data on CO₂ elimination are accompanied by a concomitant removal and significant reduction of creatinine or urea, as previously shown by others.^{18,19,21,34} This means that ADVOS might be used for COVID-19 Patients with CO₂ removal problems. Indeed, the correction of acid-base imbalances (and hypercapnia is one of those) is an indication for the therapy. This is independent of the presence of AKI. In contrast to the other dialysis methods that add mainly bicarbonate, ADVOS "mimics" what the kidney does and removes CO₂ directly (as H⁺ and HCO₃⁻), thus supporting the renal compensation of respiratory acidosis.^{20,31-33} The question here is to decide whether an AKI diagnosis is necessary if the kidney is not able to provide an adequate renal compensation. Moreover, the need of CO₂ removal is independent of the triggering cause of ARDS. Thus, ADVOS might be considered for non-COVID-19 patients with decarboxylation problems, as already described by Fuhrmann et al.¹⁸

Our study poses several limitations. Firstly, our cohort is limited by the low number of patients, which does not allow further conclusions on survival or outcomes. Secondly, the absence of a control group additionally limits our study. Thirdly, the optimal time point to start an ECCO₂R treatment is still not evaluated. We started the ADVOS therapy once patients had been on mechanical ventilation for at least 72 hours, which could have already led to the development of VILI and the deterioration of other systems through organ cross-talk mechanisms.³⁵⁻³⁷ Subsequently, a combination of mechanical ventilation and renal replacement therapy has been shown to increase mortality rates in COVID-19 patients up to 73% y.³⁸ Finally, our results are restricted to a specific population of COVID-19 patients with advanced stage of the disease suffering from moderate to severe ARDS on mechanical ventilation. In the specific case of COVID-19, further data are still needed to comprehend how these patients can benefit from extracorporeal therapy.

5 | CONCLUSION

In conclusion, it was feasible to remove CO₂ using the ADVOS system in our cohort of COVID-19 patients with acute respiratory distress syndrome and multiorgan failure. This efficient removal of CO₂ was achieved at low flows up to 300 mL/min using a conventional hemodialysis catheter and without a membrane lung or a gas phase. In addition, acid-base balance correction and creatinine and BUN levels decrease were achieved already within the first treatment. Further studies are needed to demonstrate whether the effects of the ADVOS therapy and those of carbon dioxide removal can help to reduce the burden of mechanical ventilation by either reducing the time of ventilation or favoring an ultraprotective ventilation.

CONFLICT OF INTEREST

TL received travel grants from Gilead, Pfizer, and MSD. The other authors declare no conflict of interest.

AUTHORS CONTRIBUTIONS

Julia Allescher, Sebastian Rasch and Tobias Lahmer conceived the study. Julia Allescher, Sebastian Rasch, Johannes R. Wiessner, Christina Huberle, Felix Hesse, Dominik Schulz, Wolfgang Huber, Tobias Lahmer contributed to acquisition of the data. Julia Allescher, Sebastian Rasch, Tobias Lahmer and Aritz Perez Ruiz de Garibay analysed the data and interpreted the results. Julia Allescher, Sebastian Rasch and Tobias Lahmer wrote the manuscript. Julia Allescher, Sebastian Rasch, Johannes R. Wiessner, Christina Huberle, Felix Hesse, Dominik Schulz, EH, Roland M. Schmid, Wolfgang Huber, Tobias Lahmer revised it critically for important intellectual content. All authors agree with the article submission. All authors read and approved the final manuscript.

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