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MAIN TEXT

Integration of sustained low-efficiency dialysis into extracorporeal membrane oxygenation circuit in critically ill COVID-19 patients—A feasibility study

Frederic Arnold[1,2,3] | **Rika Wobser**[1] | **Johannes Kalbhenn**[4] | **Lukas Westermann**[1]

[1]Department of Medicine IV, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[2]Institute for Microbiology and Hygiene, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[3]Berta-Ottenstein-Programme for Clinician Scientists, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[4]Anesthesiology and Critical Care, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Correspondence
Johannes Kalbhenn, Anesthesiology and Critical Care, Medical Center, Faculty of Medicine, University of Freiburg, Hugstetter Strasse 55, 79106, Freiburg, Germany.
Email: johannes.kalbhenn@uniklinik-freiburg.de

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Abstract

Background: Severe COVID-19 can necessitate multiple organ support including veno-venous extracorporeal membrane oxygenation (vvECMO) and renal replacement therapy. The therapy can be complicated by venous thromboembolism due to COVID-19-related hypercoagulability, thus restricting vascular access beyond the vvECMO cannula. Although continuous renal replacement therapy can be performed via a vvECMO circuit, studies addressing sustained low-efficiency dialysis (SLED) integration into vvECMO circuits are scarce. Here we address the lack of evidence by evaluating feasibility of SLED integration into vvECMO circuits.

Methods: Retrospective cohort study on nine critically ill COVID-19 patients, treated with integrated ECMO-SLED on a single intensive care unit at a tertiary healthcare facility between December 2020 and November 2021. The SLED circuits were established between the accessory arterial oxygenator outlets of a double-oxygenator vvECMO setup. Data on filter survival, quality of dialysis, and volume management were collected and compared with an internal control group receiving single SLED.

Results: This study demonstrates general feasibility of SLED integration into existing vvECMO circuits. Filter lifespans of ECMO-SLED compared with single SLED are significantly prolonged (median 18.3 h vs. 10.3 h, $p < 0.01$). ECMO-SLED treatment is furthermore able to sufficiently normalize creatinine, blood urea nitrogen, and serum sodium, and allows for adequate ultrafiltration rates.

Conclusions: We can show that ECMO-SLED is practical, safe, results in adequate dialysis quality and enables sufficient electrolyte and volume management. Our data indicate that SLED devices can serve as potential alternative to continuous-veno-venous-hemodialysis for integration in vvECMO circuits.

KEYWORDS

COVID-19, ECMO, ECOS, MOF, RRT, SLED

1 | INTRODUCTION

COVID-19 is caused by an infection with the SARS-CoV-2 virus. Although the majority of infections lead to mild or no symptoms, some patients develop pneumonia.[1] Severe pneumonia can result in acute respiratory distress syndrome (ARDS).[2] Despite the predominance of respiratory manifestations, hospitalized COVID-19 patients are under high risk for concomitant acute kidney injury (AKI).[3] This risk increases in critically ill COVID-19 patients treated on intensive care units and especially in patients requiring extracorporeal organ support (ECOS).[4] A combination of severe pneumonia and AKI can necessitate initiation of ECOS consisting of extracorporeal-membrane oxygenation (ECMO) and renal replacement therapy (RRT).

Multi-organ support is standard procedure for tertiary care centers with respective experience. However, the establishment and maintenance of simultaneous ECOS in critically ill COVID-19 patients can be challenging. Hypercoagulability is known to be associated with severe COVID-19, increasing the risk for thromboembolic complications and reducing RRT filter lifespans.[5,6] Artificial surfaces of venous catheters can additionally trigger procoagulatory factors. In case of venous thromboembolic events, insertion sites for central venous catheters necessary for simultaneous ECOS can be limited. In worst case, establishment of ECMO and RRT via independent vascular accesses is not feasible. In these patients, the integration of an RRT device into the ECMO circuit is mandatory.

Studies have shown at least non-inferiority concerning filter lifespans and effectiveness of solute removal and ultrafiltration compared with independent ECMO and RRT circuits.[7,8] However, past studies have focused on the integration of continuous RRT (continuous veno-venous hemodialysis, CVVHD) into ECMO circuits.[9] In contrast, evidence for the integration of sustained low-efficient dialysis (SLED) into ECMO circuits is scarce. This is surprising because SLEDs are widely used for RRT and non-inferior compared with continuous RRT procedures.[10,11] Although the concept of an integrated ECMO-SLED is mentioned in literature, evidence lacks beyond anecdotal notion.[12–14]

Evidence concerning feasibility of an integrated ECMO-SLED is especially pressing because outbreaks of COVID-19 can lead to regional shortages in RRT devices and staff.[15,16] Consequently, ECOS experienced centers involved in the treatment of severe COVID-19 will profit from a study addressing the integration of SLED into an ECMO circuit. In this report, we show that in a subset of critically ill COVID-19 patients with restricted vascular access and need for ECMO-RRT, SLED integration into ECMO circuits is practical, safe and results in adequate solute and fluid removal.

2 | METHODS

2.1 | General information

In this single-center retrospective feasibility study, we report data of nine patients from the University of Freiburg Medical Center, division of Anesthesiology and Intensive Care, Freiburg, Germany. Patients were adults (aged 18 years or older) with a laboratory-confirmed SARS-CoV-2 infection. All patients required vvECMO and RRT therapy due to multiorgan failure during severe COVID-19. All patients were treated on the same intensive care unit following identical standard operating procedures between December 2020 and November 2021. Demographic data, past medical history, clinical findings, laboratory values, treatment details, and outcome data of patients were extracted from electronic patient records by the investigators of the study (FA, JK, and LW). All data were reviewed and verified by two physicians (FA and LW). Any uncertain records were not included in the final data analysis. This study is in conformity with the ethical principles for medical research involving human subjects as laid down in the Helsinki Declaration (1964) and its amendments. Analysis and publication of the data were approved by the local ethics committee (405/20 to JK).

2.2 | ECMO and hemodialysis treatments

Veno-venous ECMO (vvECMO) was applied in COVID-19-associated ARDS. Decision to initiate vvECMO was individually made after multidisciplinary discussion. Vascular access for vvECMO was established using a transjugular two-stage Avalon Elite® catheter (Maquet Holding GmbH & Co. KG, Rastatt, Germany). The vvECMO circuit was composed by a Revolution® Centrifugal Blood Pump operated by the Stöckert Centrifugal Pump Console (SCPC), two EOS ECMO™ oxygenators (all LivaNova Deutschland, Munich, Germany) and a Sechrist 3500CP-G gas blender (Sechrist Industries, Inc., Anaheim, CA, U.S.A.). A vvECMO setup with two oxygenators connected in parallel after the centrifugal pump is standard of care for severe ARDS at our center. The system setup allows blood flow up to 7 L/min. Usually vvECMO was adjusted to a blood flow of 3–5 L/min. Daily inspection of the pump and oxygenators, with special regard to thrombotic scaling, was performed by perfusionists. Extracorporeal components were changed exclusively when the function was impaired. No scheduled changes were applied.

SLED treatments were performed with the GENIUS®90 single-pass batch system (Fresenius Medical Care GmbH, Bad Homburg, Germany) using suitable tubing kits and dialyzers. Dialysate solutions were individually prepared

at site. The GENIUS®90 SLED system uses a single double-sided roller pump that simultaneously generates blood (Q_B) and dialysate flow (Q_D) in a fixed ratio. To achieve treatment times up to 24 h, tubing kits allowing Q_B:Q_D ratios of 2:1 were used. Blood flow rates between 50 and 300 ml/min, corresponding dialysate flow rates of 25–150 ml/min and ultrafiltration rates between 100 and 1000 ml/h were chosen per treatment at the discretion of the treating physician. The SLED circuit was integrated between the sampling outlets of the oxygenators. SLED systems were used until dialysate was saturated or visual inspection of the dialysis filter indicated clotting events and prompted treatment termination. Figure 1 gives an overview of the ECMO-SLED setup. In case of SLED maintenance after vvECMO explantation, a standard 11F double lumen dialysis catheter was implanted in the jugular vein.

Anticoagulation was performed with the low-molecular-weight heparin (LMWH) enoxaparin. Anticoagulation with LMWH was maintained by subcutaneous injection of enoxaparin in a bodyweight-adapted individual dose once or twice a day. Sufficient anticoagulation was supposed with an anti-factor-Xa activity of 0.25–0.5 IU/ml determined 4 h after enoxaparin injection. Before connection of SLED to the vvECMO, an initial bolus of 1000 I.U. enoxaparin was added to the priming fluid of the SLED system. This protocol has been published recently and was associated with superior RRT circuit patency in severe COVID-19.[17]

2.3 | Laboratory procedures

Laboratory confirmation of SARS-CoV-2 infection was performed with real-time RT-PCR methods from throat swab samples. Concentrations of creatinine and blood urea nitrogen (BUN) were assessed in serum samples. Anti-factor-Xa activity and activated partial thromboplastin time (aPTT) were measured in citrate blood samples during hospitalization. Potassium- and sodium levels were assessed by point-of-care blood gas analyses. AKI was diagnosed according to the respective KDIGO clinical practice guidelines.[18]

2.4 | Statistical analysis

Categorical variables were presented as *n* (%). Continuous variables were presented as median (IQR) or mean (SD), if not indicated otherwise. Wilcoxon–Mann–Whitney tests were performed to calculate *p*-values. Comparison of dialysis filter survival were presented as Kaplan–Meier estimators and compared applying the Mantel–Cox test. A two-sided α of less than 0.05 was considered statistically

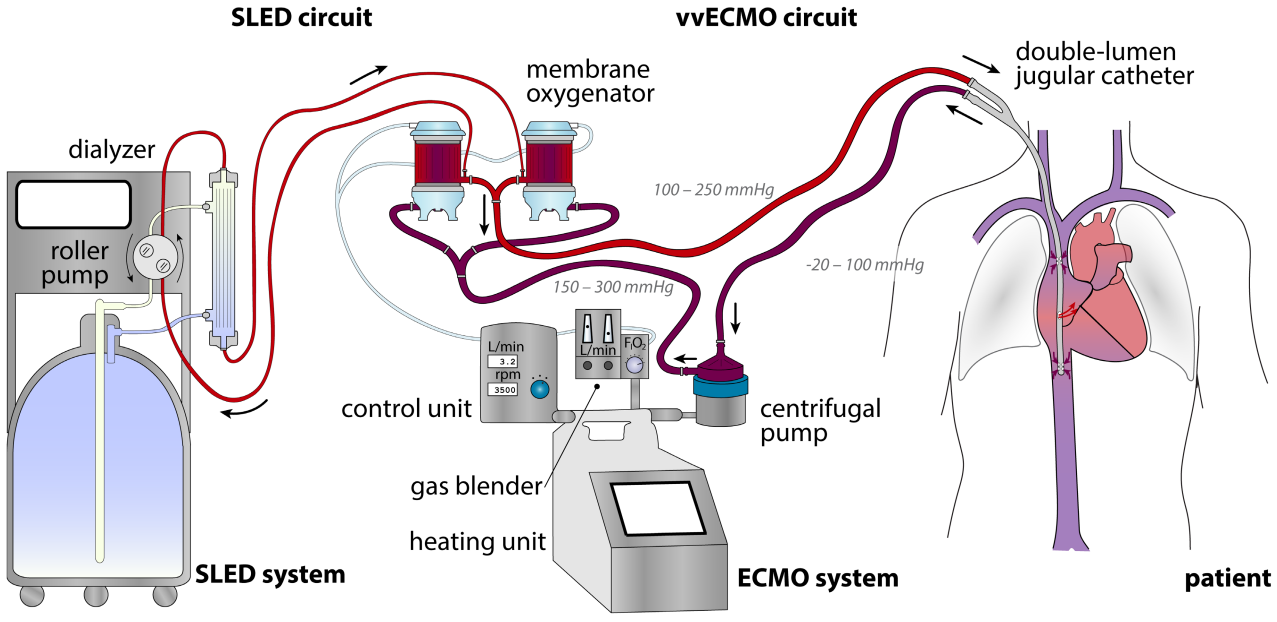

FIGURE 1 Schematic of sustained low-efficiency dialysis (SLED) integration within the veno-venous extracorporeal membrane oxygenation (vvECMO) circuit. Vascular access is provided by a single double lumen central venous catheter. The vvECMO circuit consists of a centrifugal pump operated by an ECMO console regulating blood flow by adjusting the pump speed. Blood is pumped through two ECMO oxygenators connected in parallel to the pump outlet. Oxygenation and decarboxylation are regulated via a gas blender controlling gas flow and oxygen concentration. The integrated SLED circuit is established between the accessory arterial oxygenator outlets

significant. All statistical analyses were performed using Prism (Version 9.1.3), GraphPad Software, San Diego, California, USA.

3 | RESULTS

In this retrospective single-center study, we share results from nine patients, treated with integrated vvECMO-SLED due to intermittent shortages of CVVHD devices and limited vascular access options. The vvECMO-SLED setup is described in the methods section and illustrated in Figure 1. Four of the nine patients required continuation of SLED treatments after vvECMO weaning and serve as an internal control group. The primary aim of this study was to investigate the feasibility of ECMO-SLED in critically ill COVID-19 patients.

The patients had a mean age of 49 years (SD ± 9.2 years) with an equal sex distribution (female: 56%) (Table 1). The mean body mass index was elevated in the obese range (31.1 kg/m^2, SD ± 5.3 kg/m^2). A history of cardiac disease or diabetes mellitus type 2 was present in six patients (67%), respectively. Mean treatment time with vvECMO was 13.4 days (SD ± 4.5 days). Mean treatment time of simultaneous ECMO-SLED was 7.9 days (SD ± 5.8 days). The mean blood flow rate (Q_B) of integrated SLED was 123.1 ml/min (SD ± 23.7 ml/min). Due to the single pump SLED system, dialysate flow rates (Q_D) were half as high as blood flow rates (Q_B:Q_D = 2:1). The mean ultrafiltration rate (UF) was 141.8 ml/h (SD ± 74.33 ml/min).

TABLE 1 Baseline characteristics of cohort treated with ECMO-SLED

	n = 9
Mean age, years (SD)	49 (9.2)
Female, *n* (%)	5 (56)
Body mass index, kg/m^2 (SD)	31.1 (5.3)
vvECMO, d (SD)	13.4 (4.5)
SLED w/ vvECMO, d (SD)	7.9 (5.8)
Mean SLED Q_B, ml/min (SD)	123.1 (23.7)
Mean SLED UF, ml/min (SD)	141.8 (74.3)
Vasopressors, *n* (%)	9 (100)
Dexamethasone, *n* (%)	6 (67)
Non-renal comorbidities	
Pulmonary, *n* (%)	0 (0)
Cardiac, *n* (%)	6 (67)
Malignancy, *n* (%)	1 (11)
Diabetes mellitus, *n* (%)	6 (67)
Renal	
Creatinine, baseline, mg/dl (SD)	1.0 (0.5)
Acute kidney injury ≥ stage 1, *n* (%)	9 (100)
Creatinine max, mg/dl (SD)	4.71 (2.3)
Pulmonary embolism, *n* (%)	3 (33)
Intracranial complications (hemorrhage/ischemia), *n* (%)	0 (0)
Extracorporeal bleeding events, *n* (%)	0 (0)
Death, *n* (%)	6 (67)

Abbreviations: Q_B, SLED blood flow rate; UF, SLED ultrafiltration rate.

The patients did not suffer from advanced chronic kidney disease (baseline creatinine 1.0 mg/dl, SD ± 0.5 mg/dl). All patients developed COVID-19-associated AKI with a mean creatinine level of 4.7 mg/dl (SD ± 2.3 mg/dl) prior to SLED initiation. We observed pulmonary embolism in three patients (33%). We did not observe any major intra- or extracorporeal bleeding events or intracerebral complications. Six patients died (67%).

Filter lifespan is a major factor of RRT feasibility. Insufficient anticoagulation and low flow significantly reduce this lifespan. Median filter lifespan in our cohort was 18.3 h (IQR: 10.7–21.5 h), observed in 75 SLED treatments with SLED integrated into the vvECMO circuit (ECMO-SLED group). Median filter lifespan of 84 SLED treatments of a subcohort of four patients after vvECMO explantation (SLED-group) was significantly lower with 10.3 h (IQR: 5.4–18.5 h, $p < 0.01$) (Figure 2A,B). The same difference in filter lifespans can be observed, limiting the comparison with the four patients receiving ECMO-SLED and SLED after vvECMO explantation (Figure S1). The characteristics of the SLED-subgroup are shown in Table S1.

Despite longer filter survival, mean anti-Xa-levels in the ECMO-SLED group were significantly lower than in the SLED group (0.28 IU/ml vs. 0.74 IU/ml, $p < 0.01$) (Figure 2C). Comparison of aPTT showed mean values slightly above the normal range in both groups. ECMO-SLED patients showed a 3.3 s longer aPTT (Figure S2).

Elevated creatinine and BUN levels were sufficiently reduced. Creatinine was lowered by 1.4 mg/dl (2.7 mg/dl vs. 1.3 mg/dl, $p < 0.01$), BUN by 58.5 mg/dl (118.3 mg/dl vs. 59.8 mg/dl, $p < 0.01$) by SLED operated in the vvECMO circuit (Figure 3A–D). All patients treated with ECMO-SLED developed oliguria or anuria prior to and during ECMO-SLED treatment (Figure S3).

In addition, ECMO-SLED was able to control potassium levels within normal range (Figure 3E,F). Hypernatremia—often associated with severe COVID-19—was normalized after SLED integration into the vvECMO circuit (148.1 mmol/L vs. 142.5 mmol/L, $p < 0.01$) (Figure 3G,H).

ECMO-SLED allowed adequate and non-inferior ultrafiltration rates compared with the SLED-group. Balanced volume management was achieved (Figure S4).

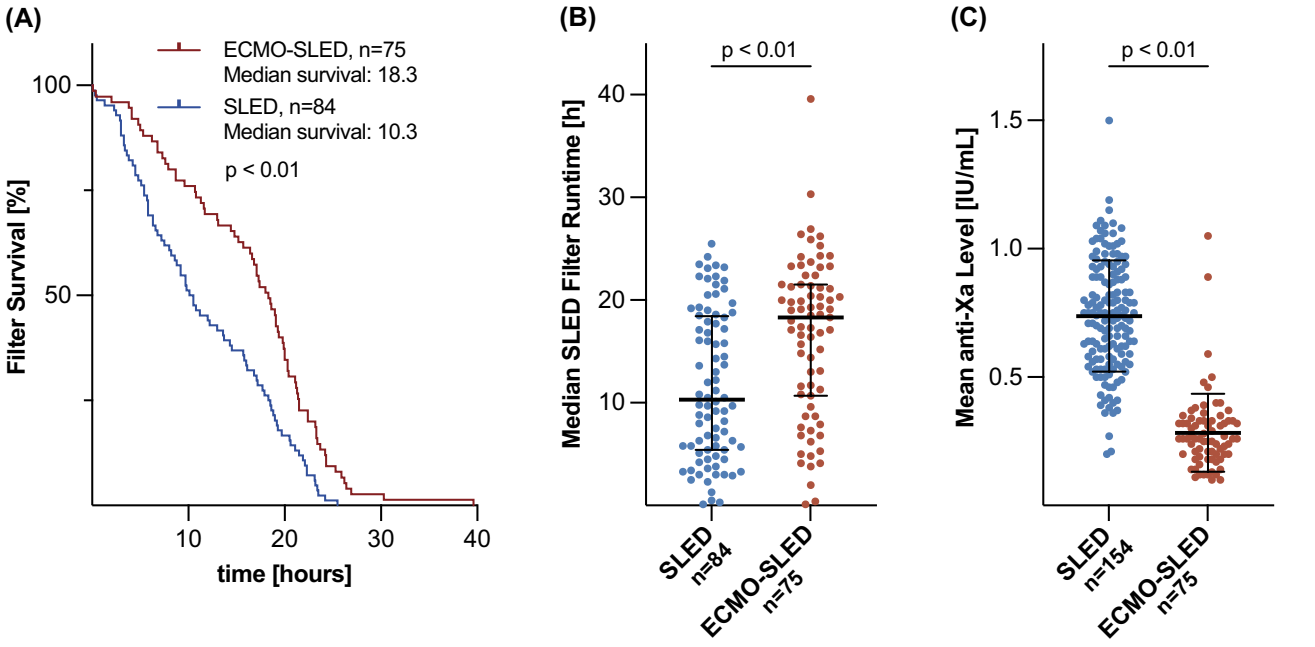

FIGURE 2 Extracorporeal-membrane oxygenation–sustained low-efficiency dialysis (ECMO-SLED) leads to non-inferior filter lifespans despite low anti-Xa-levels. (A) Kaplan–Meier estimators of filter survival in hours. Blue line (▬) depicts isolated SLED circuits. Red line (▬) depicts SLED circuits integrated into a veno-venous extracorporeal membrane oxygenation setup. *p*-value calculated using MantelCox test. (B) Median filter runtimes in the SLED (●) and ECMO-SLED (●) group. Whiskers depict IQR, *p*-value calculated using Wilcoxon–Mann–Whitney test. (C) Comparison of mean anti-Xa levels. Whiskers depicting SD, *p*-value calculated using Wilcoxon–Mann–Whitney test

4 | DISCUSSION

Severe COVID-19 ARDS poses a significant risk for AKI.[19] Volume overload often additionally aggravates ARDS and must be addressed to allow for pulmonary recompensation and vvECMO weaning. Because many medical centers provide RRT devices for prolonged intermittent RRT such as SLED, these devices should be regarded as an alternative treatment option for integrated ECMO-RRT. SLED devices offer the advantage of broad availability, rapid and easy installation, low maintenance time, plannable filter downtimes, and are more cost-effective.[11] For these reasons, they are an attractive alternative for the treatment of patients requiring combined extracorporeal organ support.

In this single-center study of nine critically ill COVID-19 patients, we show that SLED integration into the vvECMO circuit is (i) technical feasible, (ii) provides adequate dialysis quality, (iii) is able to control electrolyte disturbances, and (iv) allows for sufficient fluid balance.

The integration of SLED into vvECMO circuits has several advantages. Firstly, RRT can be performed in absence of an alternative vascular insertion site besides the double lumen cannula used for vvECMO. Therefore, integration of SLED into the existing vvECMO circuit can be a life-saving treatment option in case of limited vascular access. Because our center favors the use of two oxygenators, we were able to connect the SLED circuit quite easily at both oxygenators in the high-pressure part of the ECMO. This arrangement decreases the risk for air embolism. Secondly, each central line poses a risk for complications due to the insertion procedure (e.g., local trauma, pneumothorax, bleeding, air embolism due to ECMO-associated negative central venous pressure as well as central line–associated infection or thrombosis).[20] Often inguinal insertion sites have to be chosen, because jugular veins are already used for vvECMO, further aggravating the risk for infectious complications. Thirdly, handling of the patient (e.g., prone positioning, mobilization, nursing) is most likely facilitated with a single extracorporeal circuit. Fourthly, an integrated ECMO-SLED circuit allows for higher and stable blood flow rates within the SLED circuit. The risk for central line dysfunction of a separate RRT catheter is, therefore, not present after SLED integration into the vvECMO circuit. Constant blood flow-rates can reduce the risk of clotting events and premature termination of SLED. We therefore compared filter lifespans between patients with an integrated ECMO-SLED circuit to a subgroup of patients receiving isolated SLED after vvECMO weaning. ECMO-SLED filter lifespans were significantly higher compared with isolated SLED. The improved filter lifespan observed in the ECMO-SLED cohort is most likely attributable to a reduction of low-flow phases within

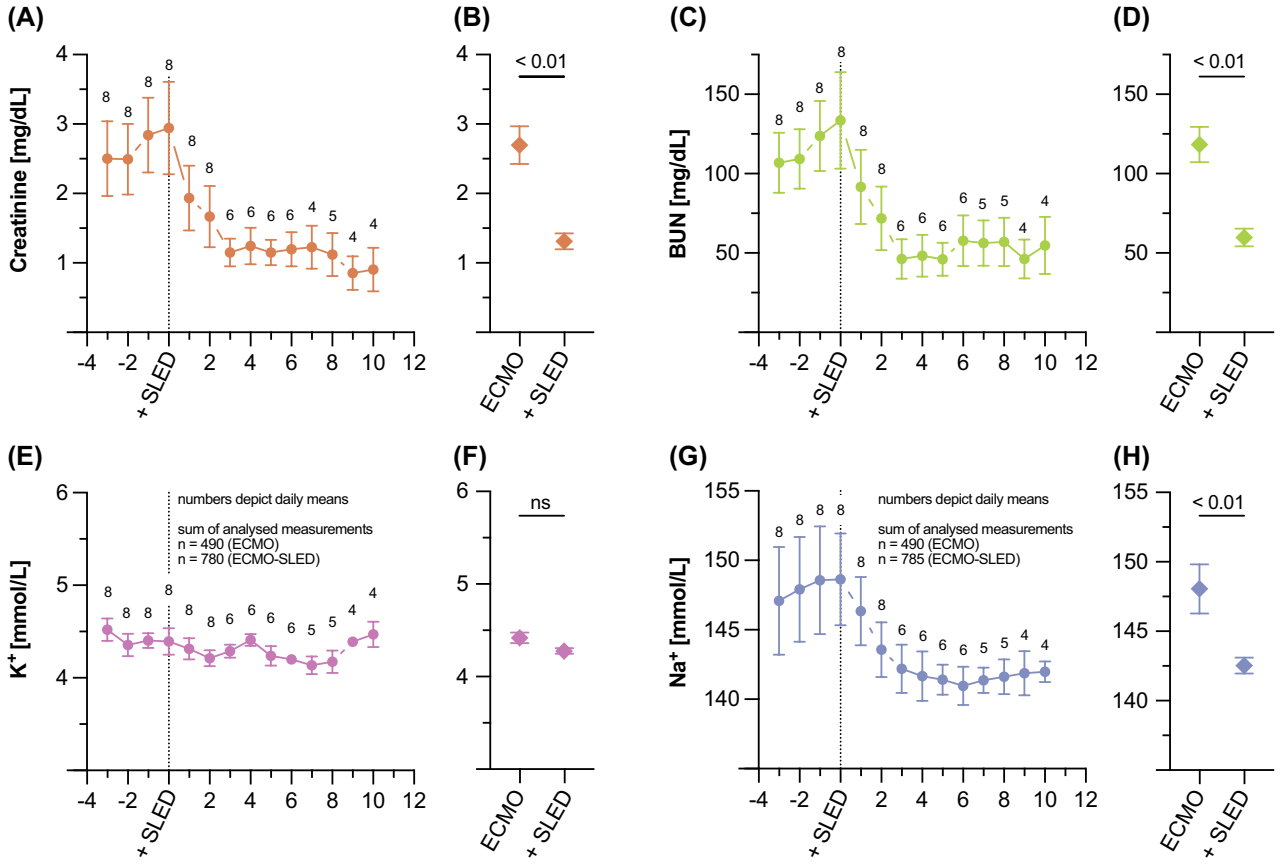

FIGURE 3 Extracorporeal-membrane oxygenation–sustained low-efficiency dialysis (ECMO-SLED) allows for sufficient dialysis. Time courses of creatinine (A), blood urea nitrogen (BUN) (C), potassium (E) and sodium (G) levels prior to and after SLED integration into the veno-venous extracorporeal membrane oxygenation circuit. Numbers indicate patients with available data sets at respective time point. Adjacent graphs compare the means of creatinine (B), BUN (D), potassium (F) and sodium (H) levels before and after SLED initiation. Bars and whiskers depict mean and SEM. *p*-values were calculated using Wilcoxon–Mann–Whitney test

the SLED circuit due to constant positive pressure in the vvECMO circuit. Our finding is in line with a previous study investigating filter lifespans in ECMO-CVVHD. Integrated ECMO-CVVHD also allowed for longer filter lifespans, compared with isolated circuits.[7] Of note, the increased filter lifespans were observed under less effective anticoagulation, as demonstrated by lower factor anti-Xa levels in the ECMO-SLED cohort. Although we found aPTT to be 3.3 s longer in the ECMO-SLED cohort compared with patients treated with isolated SLED, all measured aPTTs were just slightly above the physiological range and the small difference is most likely without biological impact. Furthermore aPTT levels are not suitable for monitoring anticoagulation with LMWHs. In our study anticoagulation was performed exclusively with the LMWH enoxaparin. Anticoagulation with LMWH has been shown to be superior in CVVHD and SLED alike in cohorts of critically ill COVID-19 patients.[17,21] We believe that constant blood flow through a combined ECMO-SLED circuit might require an even less rigorous anticoagulation regimen. Less anticoagulation may reduce the risk for common bleeding complications during vvECMO treatment.

There are also disadvantages of an integrated ECMO-SLED approach, favoring separate extracorporeal circuits: A separate SLED circuit may reduce the risk for vvECMO complications due to turbulences or clotting events in the SLED circuit. Maintenance of the SLED circuit does not have to be performed by ECMO trained staff. Furthermore, integrated SLED functionality may be limited by high circuit pressures if vvECMO blood flow rates need to be elevated (Table 2).

Besides general feasibility, we investigated dialysis quality in this study. Dialysis parameters (blood and dialysate flow) were within the standard range of SLED therapy. Our data show adequate reduction of both creatinine and BUN over time. Thus, ECMO-SLED allows for adequate hemodialysis quality. In addition, ECMO-SLED was able to control electrolyte disorders. Hypernatremia is associated with higher mortality in

TABLE 2 Advantages of SLED integration into vvECMO circuit

Integrated ECMO-SLED circuit	Separate ECMO and SLED circuits
No separate central venous catheter for RRT required • feasible in case of limited vascular access options (e.g., due to thrombosis, bleeding risk) • reduced risk of complications associated with central catheter insertion (e.g., pneumothorax, local trauma, bleeding, risk for air embolism) • reduced risk for central line associated complications (e.g., infection, thrombosis)	RRT can be maintained independently • lower risk for vvECMO circuit complications • no ECMO trained personnel required for SLED circuit service
Higher blood flow rates in SLED circuit can be maintained • better filter lifetime, less clotting events, reduced therapy downtime • less anticoagulation required	SLED not exposed to critical circuit pressure • less pressure alarms • lower risk for hemolysis due to flow turbulences
Better mobilization (e.g., prone positioning) and care of the patient with a single integrated extracorporeal circuit	Regional anticoagulation possible (citrate dialysis)

critically ill COVID-19 patients and was also present in our cohort prior to ECMO-SLED initiation.[22] SLED treatment in the vvECMO circuit was efficient to normalize hypernatremia.

Lastly, we investigated ultrafiltration rates of ECMO-SLED. Because oliguria or anuria persisted during the critical illness phase, ultrafiltration was required in all patients. Our results show that ECMO-SLED allows for a wide range of desired daily ultrafiltration rates and, thus, is able to provide adequate volume control, which is especially necessary for successful pulmonary recovery and vvECMO weaning.

This study has several limitations. Major limitations are the small sample size, its retrospective design, short observational period and the lack of a matched control group being treated with ECMO and SLED through individual vascular accesses. Data of a cohort of nine patients does not allow general conclusions for a broader population. However, the baseline characteristics, incidence of pulmonary embolism and the observed fatality rate of our cohort was in line with other reports on critically ill COVID-19 patients.[23,24] Furthermore, the primary aim of this study was to demonstrate feasibility of an integrated ECMO-SLED approach.

To allow more precise conclusions, prospective follow-up studies with a higher sample size should be conducted to further investigate safeness, filter lifespans, requirement for anticoagulation, quality of dialysis, and long-term renal outcome of the ECMO-SLED approach. Furthermore we exclusively report data from multiorgan failure due to severe COVID-19. However, we believe that the concept of an integrated ECMO-SLED is transferable to other situations of multi organ failure requiring parallel ECMO and RRT as well. Finally, data reported from our center was generated using two parallel oxygenators in the vvECMO circuit. This setup is well established and standard operating procedure at our intensive care department.[25] Two oxygenators provide several advantages such as the possibility of exchanging an oxygenator without stopping the ECMO pump, an increased blood flow of up to 7 L/min and an easy integration of SLED into the vvECMO circuit as illustrated in Figure 1. Many other centers routinely use single oxygenators in ECMO circuits. However, the concept of ECMO-SLED is also feasible in single oxygenator vvECMO circuits by integrating two luer-lock-connection sites within the post-pump-part of the circuit.

In summary, this report shows that an integrated ECMO-SLED approach is technically feasible, safe and allows for adequate dialysis quality and fluid control. Constant blood flow and sufficient pressure in the SLED circuit could improve filter lifespans and might allow reduction of anticoagulation. This feasibility study can be regarded as foundation for future research investigating ECMO-SLED as potential alternative to more established protocols like ECMO-CVVHD. High availability, cost efficiency, and low maintenance requirements of SLED devices compared with CVVHD devices are appealing arguments to further investigate our strategy.

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(2016_Kolleg.03), Bad Homburg, Germany. Our deepest sympathy goes to all our patients and their relatives who were severely affected by COVID-19. We also want to express our sincere gratitude to our fellow health-care professionals who are providing outstanding patient care during this global health crisis, despite considerable personal risk.

CONFLICT OF INTEREST

Nothing do declare.

AUTHOR CONTRIBUTIONS

Frederic Arnold, Johannes Kalbhenn, and Lukas Westermann conceived the study and its design, had full access to the patient records, and take responsibility for the accuracy and integrity of the data. Frederic Arnold and Lukas Westermann screened the electronic patient records, organized the data and performed statistical analysis. Johannes Kalbhenn and Rika Wobser critically contributed to data analysis. Frederic Arnold, Rika Wobser, Johannes Kalbhenn, and Lukas Westermann drafted the manuscript. Frederic Arnold and Lukas Westermann generated the figures. Illustrations were generated by Frederic Arnold. Rika Wobser and Johannes Kalbhenn were involved in clinical management of the patients and contributed to data interpretation. Frederic Arnold, Rika Wobser, Johannes Kalbhenn, Lukas Westermann critically revised the drafted manuscript and approve of the submission.

ETHICS APPROVAL

Analysis and publication of the data were approved by the ethics committee (405/20) of the University of Freiburg Medical Center, University of Freiburg, Faculty of Medicine, Germany.

DATA AVAILABILITY STATEMENT

The fully anonymized raw data sets analyzed in this study are available from the corresponding authors on reasonable request.

ORCID

Johannes Kalbhenn https://orcid.org/0000-0001-7551-5082
Lukas Westermann https://orcid.org/0000-0002-3525-3767

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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