Weaning from prolonged veno-venous extracorporeal membrane oxygenation (ECMO) after transfer to a specialized center: a retrospective study

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Abstract

Veno-venous extracorporeal membrane oxygenation (vvECMO) is increasingly used as rescue therapy in severe respiratory failure. In patients with pre-existent lung diseases or persistent lung injury weaning from vvECMO can be challenging. This study sought to investigate outcomes of patients transferred to a specialized ECMO center after prolonged ECMO therapy. We performed a retrospective analysis of all patients admitted to our medical intensive care unit (ICU) between 01/2013 and 12/2016 who were transferred from an external ICU after > 8 days on vvECMO. 12 patients on ECMO for > 8 days were identified. Prior to transfer, patients underwent ECMO therapy for 18 ± 9.5 days. Total time on ECMO was 60 ± 46.6 days. 11/12 patients could be successfully weaned from ECMO, 7/12 in the first 28 days after transfer (8 ± 8.8 ECMO-free days at day 28). In 7 patients, ECMO could be terminated after at least partial lung recovery, in 4 patients after salvage lung transplant. No patient died or needed re-initiation of ECMO therapy at day 28. In summary, weaning from vvECMO was feasible even after prolonged ECMO courses and salvage lung transplant could be avoided in most cases. Patients may benefit from transfer to a specialized ECMO center.

Keywords ECMO · Weaning · ARDS · Respiratory failure · Lung failure · Lung transplant

Introduction

In the context of invasive mechanical ventilation (IMV), the management of weaning is acknowledged as a complex process and an integral part of modern intensive care. Standardized weaning protocols are widely used and the institutionalization of specialized reference centers for patients difficult to wean from IMV is well established. In contrast, current knowledge about weaning from veno-venous extracorporeal membrane oxygenation (vvECMO) is sparse. In recent years, utilization of vvECMO as a rescue therapy in lung failure has been increasing worldwide [1, 2]. Notably, vvECMO is also used in patients with pre-existent lung disease in cases of acute-on-chronic respiratory failure [3]. Bridging to recovery in its narrow sense is not always feasible in these patients [3]. Thus, weaning from vvECMO in patients with pre-existent lung disease or residual lung injury after initial resuscitation becomes a growing challenge.

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In this retrospective study, we analyzed a series of patients who were referred to our center after more than 8 days on vvECMO for ECMO weaning with the possibility of salvage lung transplant (LTX).

Methods

Study setting and design

All patient data presented in this study were acquired at the Saarland University Medical Center, a tertiary care hospital and supra-regional ECMO center in southwest Germany. The setting of the study was the medical ICU of the Department of Pneumology, Allergology and Critical Care Medicine at Saarland University Medical Center. Patient registries were screened for patients admitted between 01/2013 and 12/2016 meeting the following criteria: (i) patient underwent vvECMO, (ii) vvECMO was initiated at an ICU other than the study center ICU, (iii) vvECMO duration prior to transfer to the study center ICU was more than 8 days. Patients on veno-arterial ECMO, hybrid configurations and low flow vvECMO for carbon dioxide removal were not analyzed. The following variables were analyzed at the time of presentation (day 1), day 2, day 5, and immediately prior to (day x) and/or at day 1 (day $x + 1$) after termination of ECMO therapy: ECMO parameters (blood flow, sweep gas flow), ventilator settings [inspiratory plateau pressure (P_{insp}), positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FIO_2)], and laboratory parameters [C-reactive protein (CRP), hemoglobin (Hb), white blood cell count (WBC), lactate, P_aO_2 , P_aCO_2 , pH]. In addition, total fluid balance from the time of presentation to the time of ECMO termination was determined. To assess outcomes, the following parameters were evaluated: successful weaning from ECMO at day 28 after bridging to recovery, termination of ECMO after salvage LTX, ECMO-free days at day 28, mortality at day 28, in-hospital mortality, and recurrent need for ECMO therapy at day 28 and in-hospital. The necessity for informed consent was waived by the institutional review board (Ärztchamber des Saarlandes) due to the retrospective nature of the study.

ECMO weaning

ECMO weaning was managed upon individual order of the treating intensivist in charge. Generally, the following guidelines were used: ECMO weaning was attempted whenever possible, with P_aO_2 , P_aCO_2 , and pH being aimed to be kept within physiological range. Generally, ECMO weaning was given priority over IMV weaning. Blood flow was gradually reduced as far as tolerable until a blood flow of about 2 lpm was reached. Sweep gas flow was reduced as far as tolerable

until a gas flow of 1 lpm was reached. In the case of stable oxygenation and absence of respiratory acidosis, sweep gas flow was stopped for a minimum of 1 h; if gas exchange remained sufficient, ECMO therapy was discontinued.

Data processing

Statistical analysis was performed using the software SPSS 24 (IBM, Armonk NY, USA). Data were analyzed using Mann–Whitney U test or Fisher's exact test, as appropriate. P values < 0.05 were considered statistically significant. Figures were created using the software Prism 5 (GraphPad Software, San Diego CA, USA).

Results

Baseline characteristics

During the defined study period, a total of 107 patients underwent vvECMO. Patients on vA-ECMO, hybrid configurations and low-flow ECMO for extracorporeal carbon dioxide removal were excluded. 32 vvECMO patients already were on ECMO at arrival, with cannulation performed either by the treating physicians of the referring hospital or by the mobile ECMO team of Saarland University Medical Center. Eventually, twelve patients were identified who underwent vvECMO for more than 8 days prior to transfer to the study center and were included to retrospective data analysis (Fig. 1a). As shown in Fig. 1b, we observed an increase of patients meeting the inclusion criteria in the last months with 8/12 patients being transferred since January 2016.

Baseline data of the study subjects are shown in Table 1. The mean age was 42.5 ± 15.29 years. Patients in whom lung recovery occurred were significantly younger than patients requiring salvage LTX or who died on ECMO. 11/12 patients were male. In 4/12 patients, lung failure initially occurred due to ARDS with no previous history of lung disease. In 8/12 patients, lung failure was caused by deterioration of a pre-existent chronic lung disease, namely interstitial lung diseases (3/12), cystic fibrosis (2/12), non-CF bronchiectasis (2/12), or chronic obstructive lung disease (1/12). At the time of presentation at our ICU, patients already received ECMO therapy for $18 (9\text{--}35) \pm 9.5$ days. Vascular access was established via the femoral vein (drainage cannula) and the internal jugular vein (return cannula) in 11/12 patients. In one case, patient was interfaced with the extracorporeal circuit via a 24F dual lumen cannula in the left femoral vein. 11/12 patients received IMV. All patients on IMV underwent tracheostomy. One patient received continuous noninvasive ventilation. Only pressure-controlled ventilation modes were used.

Fig. 1 **a** Flow chart presenting all patients included in the present study, **b** temporal distribution of recruitments within the study period

Table 1 Baseline data

Parameter	Unit	All patients	Lung recovery	Salvage LTX or death on ECMO	<i>p</i> value
<i>N</i>		12	7	5	
Age	Years	42.5 ± 15.29	35.4 ± 15.7	52.4 ± 11.3	0.048
Male		11	6	5	1.000
ECMO duration at arrival	Days	18 ± 9.5	17 ± 9.5	19 ± 10.5	0.755
IMV		11	6	5	1.000
Tracheostomy		11	6	5	1.000
Core-10-TISS		17.5 ± 4.8	16.1 ± 3.0	19.4 ± 6.4	0.432
SAPS II		33.0 ± 8.1	33.9 ± 7.6	31.8 ± 9.5	0.876
Blood flow	lpm	3.86 ± 1.28	3.41 ± 1.30	4.49 ± 1.04	0.149
Sweep flow	lpm	6.4 ± 3.1	6.7 ± 4.0	6.0 ± 1.2	1.000
<i>P</i> _{insp}	cmH ₂ O	24.6 ± 4.5	24.3 ± 4.5	25.0 ± 5.0	0.876
PEEP	cmH ₂ O	9.9 ± 3.2	9.7 ± 3.5	10.2 ± 3.0	0.755
FIO ₂		0.70 ± 0.20	0.66 ± 0.23	0.76 ± 0.15	0.530
CRP	mg/l	93.0 ± 99.5	58.9 ± 23.3	140.7 ± 146.7	1.000
WBC	k/μl	10.4 ± 4.2	11.4 ± 5.1	9.0 ± 2.3	0.639
Lactate	mmol/l	1.2 ± 0.6	1.0 ± 0.3	1.3 ± 0.9	1.000
Hemoglobin	g/dl	9.0 ± 1.2	8.6 ± 1.1	9.5 ± 1.3	0.343
History of lung disease		8	5	3	1.000
No history of lung disease		4	2	2	1.000

Data are presented as number or mean ± SD, as appropriate. Statistical analysis was performed using the Mann–Whitney *U* test or Fisher’s exact test, as appropriate. *P* values < 0.05 (shown in *italics*) were considered statistically significant

ECMO extracorporeal membrane oxygenation, IMV invasive mechanical ventilation, TISS therapeutic intervention scoring system, SAPS II simplified acute physiology score 2nd version, *P*_{insp}: inspiratory plateau pressure, PEEP positive end-expiratory pressure, FIO₂ fraction of inhaled oxygen, CRP C-reactive protein, WBC white blood cell count

Clinical data

At the time of presentation, patients received ECMO with a blood flow of 3.86 ± 1.28 lpm and a sweep gas flow of 6.4 ± 3.1 lpm. Changes in blood and sweep gas flow over time are shown in Fig. 2. In the first 5 days upon referral, no substantial changes in either of the ECMO parameters were made. Before termination of ECMO therapy, blood flow was 1.84 ± 0.40 lpm and sweep gas flow was 1.5 ± 2.4 lpm.

Figure 3A shows changes in ventilator settings over time. At the time of presentation, patients were ventilated

with an inspiratory pressure of 24.6 ± 5.0 cmH₂O and a positive end-expiratory pressure (PEEP) of 9.9 ± 3.2 cmH₂O. FIO_2 was 0.70 ± 0.20 , as shown in Fig. 3b, with a resulting P/F ratio (defined as $\text{PaO}_2/\text{FIO}_2$) of 141 ± 73 . Ventilator settings were only marginally changed in the first 5 days, with a trend towards slight reduction of inspiratory pressure and FIO_2 . Before termination of ECMO therapy, inspiratory pressure was 20.3 ± 3.0 cmH₂O, PEEP was 6.3 ± 1.6 cmH₂O, and FIO_2 was 0.43 ± 0.13 . pH and p_aCO_2 were kept within physiological ranges during the ECMO course (Fig. 3c). After

Fig. 2 Time curves of the ECMO parameters blood flow (a) and sweep gas flow (b) in liters per minute (LPM) at the day of presentation (d1), at day 2 (d2), day 5 (d5), and before termination of ECMO therapy (dx). Data are shown as mean $\pm$ SD. $N = 12$ (d1, d2, d5) or $N = 11$ (dx)

Fig. 3 Time curves of inspiratory pressure (P_{insp}) and positive end-expiratory pressure (PEEP) (A), fraction of inspiratory oxygen (FIO_2) and P/F ratio ($\text{PaO}_2/\text{FIO}_2$) (B), pH and p_aCO_2 (C), or C-reactive protein (CRP) and hemoglobin (Hb) levels (D), respectively. Data are

shown from the day of presentation (d1), day 2 (d2), day 5 (d5), day before termination of ECMO therapy (dx), and day 1 after termination of ECMO therapy (dx+1). Data are shown as mean $\pm$ SD. $N = 12$ (d1, d2, d5) or $N = 11$ (dx, dx+1)

termination of ECMO therapy, moderate permissive hypercapnia was tolerated.

Patients in whom ECMO therapy could be terminated after successful bridging to recovery had a negative fluid balance at the time of ECMO termination (-8.8 ± 7.2 L, Table 2). Patients who underwent salvage LTX or died on ECMO had a positive mean fluid balance ($+3.2 \pm 27.9$ L). However, there was no significant difference between both groups ($p = 0.202$). As shown in Fig. 3d, CRP and Hb levels did not show consistent changes over time.

Outcomes

Upon referral, ECMO therapy was continued for 41 ($7\text{--}135$) ± 42.6 days, which resulted in a total ECMO runtime of 60 ($16\text{--}170$) ± 46.6 days (Table 2). One patient, who was not eligible for LTX, could not be weaned and died after 170 days on ECMO. 11/12 patients could be successfully weaned off ECMO. In seven patients,

weaning was possible after—at least partial—lung recovery, in four patients, ECMO therapy could only be terminated after salvage lung transplant. Of note, all patients in whom lung recovery occurred were weaned within the first 28 days upon referral. In contrast, patients who could not be weaned within the first 28 days upon referral either required salvage LTX or died. No patient died at day 28. In-hospital mortality was 16.67%. At day 28, no patient who was successfully weaned needed re-initiation of ECMO therapy. In four initially weaned patients, ECMO therapy had to be eventually re-initiated during their hospital stay; three of them underwent salvage LTX later on. 5/8 patients with pre-existent lung disease could be weaned off device. None of them needed re-initiation of ECMO therapy with 28 days. 3/8 needed ECMO later on in their course; all were successfully bridged to LTX finally. Figure 4 shows Kaplan–Meier plots of survival and ECMO duration.

Table 2 Patient outcomes and complications during ECMO

Parameters	Unit	All patients	Lung recovery	Salvage LTX or death on ECMO	<i>p</i> value
<i>N</i>		12	7	5	
ECMO duration after arrival	Days	41 ± 42.6	15 ± 7.6	79 ± 44.0	<i>0.003</i>
ECMO duration total	Days	60 ± 46.6	32 ± 14.1	98 ± 50.6	<i>0.003</i>
ECMO-free days at day 28		8 ± 8.8	13 ± 7.6	0 ± 0	<i>0.003</i>
Weaned off device at day 28		7	7	0	<i>0.001</i>
Mortality at day 28		0	0	0	
Mortality in-hospital		2	1	1	1.000
Recurrent ECMO at day 28		0	0	0	
Recurrent ECMO in-hospital		4	4	0	0.194
Lung transplantation		7	3	4	1.000
Thrombocytopenia < 50/nl		2	1	1	1.000
Thrombocytopenia < 100/nl		8	3	5	0.081
Bleeding requiring transfusion > 2 PRBC		7	2	5	<i>0.028</i>
Bleeding requiring transfusion > 4 PRBC		0	0	0	
Bleeding requiring surgical intervention		0	0	0	
Intracranial bleeding		0	0	0	
Fatal bleeding		0	0	0	
Heparin-induced thrombocytopenia ^a		0	0	0	
Venous thrombosis ^b		3	1	2	0.523
Pulmonary embolism ^c		0	0	0	
CPR		2	0	2	0.152
Fluid balance	Liters	-3.8 ± 18.7	-8.8 ± 7.2	$+3.2 \pm 27.9$	0.202

Data are presented as number or mean $\pm$ SD, as appropriate. Statistical analysis was performed using the Mann–Whitney *U* test or Fisher's exact test, as appropriate. *p* values < 0.05 (shown in italics) were considered statistically significant

ECMO Extracorporeal membrane oxygenation, PRBC packed red blood cells, CPR cardiopulmonary resuscitation

^aVerified by heparin-induced platelet aggregation test

^bVerified by ultrasonography or computer tomography

^cVerified by computer tomography

Fig. 4 Kaplan–Meier plots of **a** total survival ($N=12$); **b** survival of patients weaned after lung recovery (weaned, $N=7$) versus patients undergoing salvage LTX or died on ECMO (died or LTX, $N=5$); **c** total duration of ECMO therapy ($N=12$); **d** duration of ECMO ther-

apy in patients weaned after lung recovery (weaned, $N=7$) versus patients undergoing salvage LTX or died on ECMO (died or LTX, $N=5$)

Discussion

The main findings of our present study are: (i) weaning from vvECMO after prolonged courses is feasible, and (ii) substantial changes in the ECMO configurations in the initial phase after transfer were not achievable. In recent years, our center registered repeated requests from external hospitals seeking for referral of patients with prolonged ECMO courses, especially with regard to the possibility of salvage LTX. By their treating physicians who established ECMO, these patients were considered to suffer from “ECMO weaning failure”. In the absence of an accepted consensus definition of this term, the diagnosis of ECMO weaning failure as a reason for referral was based on the subjective impression of the treating physicians in the referring hospitals. The number of patients transferred to our center after such requests particularly increased in the last months. This retrospective study aimed to investigate the outcomes of patients referred after a history of more than 8 days on ECMO before transfer to our ICU. A total of twelve patients fulfilled the inclusion criteria; 7/12 patients were referred by university or comparable

tertiary care centers. This small cohort represents a highly selected group of relatively young patients who either had no history of lung disease and were therefore considered to have potential for lung recovery, or who were initially considered eligible for LTX.

Nowadays, ECMO is considered an established procedure in the management of hypoxemic lung failure. An epidemiologic study from Germany demonstrated an increase in the use of ECMO in respiratory failure since 2007, with 2.4 cases per 100,000 inhabitants in 2014 [2]. In this work, as well as in other published studies, duration of ECMO for respiratory support did not exceed 10 days in the majority of patients [2, 4, 5]. In the CESAR trial, which provided the strongest evidence in favor of the usage of ECMO in severe ARDS so far, median duration of ECMO therapy was 9 days [6]. A recent Korean study reported a median ECMO duration of 7.4 days in patients who could be successfully weaned [7]. However, data from the international registry of the Extracorporeal Life Support Organization showed that in 22% of the patients duration of ECMO therapy exceeded 14 days [8]. Single reports on successful weaning after exceptionally prolonged ECMO therapy exist [5, 7, 9–11].

In the present report, patients already underwent prolonged ECMO courses of 18 ± 9.5 days before arrival. ECMO was continued for additional 41 ± 42.6 days. The primary goal in all patients was bridging to recovery whenever feasible. In patients with end stage lung disease, ECMO was utilized to sustain life until salvage LTX was possible. In all patients, regardless whether they were candidates for LTX, we aimed to wean off ECMO whenever possible. 11/12 patients could be weaned successfully, seven after at least partial lung recovery, four after salvage LTX. One patient died after 170 days on ECMO. Of those weaned off device, three patients underwent LTX later on. By weaning these patients from ECMO before LTX, ECMO-related complications may be reduced and the risks of salvage LTX with ongoing ECMO therapy can be avoided. Furthermore, mobilization pre-transplant is facilitated, and a thorough reconditioning can be realized.

In the present study, it was difficult to identify specific measures that enabled successful ECMO weaning. In some cases, sufficient anti-infective management or treatment of anemia may have crucially contributed to successful ECMO weaning; however, altogether neither laboratory markers of infection nor hemoglobin levels did seem to have a prognostic effect in this small collective.

Fluid balance is increasingly recognized as an important parameter in intensive care, and positive fluid balance is associated with worse outcomes in various groups of ICU patients, especially those with sepsis and septic shock [12, 13]. In the current analysis, the weaning process of patients bridged to lung recovery included a marked negative fluid balance of -8.8 ± 7.2 L. However, there was no difference regarding fluid balance compared to patients who died or needed salvage LTX. Further studies are required to evaluate the role of fluid balance in ECMO weaning.

In contrast to countries such as the United Kingdom, where ECMO is only provided in few specialized centers, there are no such restrictions in the German healthcare system, allowing ECMO therapy also in low volume centers. There is also no obligation to disclose data on ECMO volume or outcomes. Therefore, the experience of the referring centers, which ranged from community hospitals to tertiary care and university centers, is not clear in all cases, making it difficult to identify skill differences compared to our center.

In fact, there are conflicting data on the impact of case volume on mortality of ECMO patients [14, 15]. Yet, a recently published statement by an international expert panel recommended that ECMO should only be provided by experienced centers with at least twenty cases per year [16]. Our current small hypothesis-generating report further adds the question, whether patients who already are on ECMO could benefit from a secondary transfer to a specialized ECMO center, especially if early weaning from ECMO cannot be realized. In line with the available literature on prolonged

ECMO courses, our current data suggest that gaining as much time as possible to enable native lung recovery, while preventing or managing multi-organ failure and ECMO-related complications, may be the central determinant for successful weaning in these unique cases rather than single therapeutic measures. Therefore, a thorough center experience in the general management of individuals on ECMO may contribute to keep patients alive without severe complications until lung recovery or lung transplant.

Conclusions

Patients undergoing prolonged ECMO therapy with difficult ECMO weaning represent a small and heterogeneous subset, but the relevance of this population will probably increase with the abundant use of the procedure. Therefore, ECMO-weaning protocols should be established analogous to IMV, and criteria for difficult, prolonged, and failed weaning from ECMO should be defined. In addition, future studies should aim to identify predictors for successful ECMO weaning.

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Compliance with ethical standards

Conflict of interest MK received honoraria from Getinge. The other authors declare no conflict of interest.

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