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Awake ECMO for COVID-19 Induced Acute Respiratory Distress

Syndrome

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The outcome of COVID-19 patients treated on intensive care units (ICU) is unsatisfying (1). Veno-venous extracorporeal membrane oxygenation (vv-ECMO) can serve as a rescue strategy when patients deteriorate during invasive ventilation (2, 3). Utilizing extracorporeal membrane oxygenation (ECMO) in awake patients without endotracheal intubation (awake-ECMO) has shown satisfying results in immunocompromised patients or as a bridge-to-transplant strategy (4-6), but bears ECMO-specific risks such as bleeding and – specifically in awake patients - selfinflicted lung injury (p-SILI)(7). Reports on awake-ECMO for COVID-19 are currently limited to case reports (8, 9).

We report eighteen adult patients with real-time RT-PCR-confirmed SARS-CoV-2 infection and hypoxemic COVID-19-ARDS (CARDS) supported awake on vvECMO on four German tertiary care ICUs from 1st February to 30th April 2021. During the study period, a total of 248 COVID-19 patients were hospitalized on these wards. Seventy-nine of these (31.9%) were supported with non-invasive oxygenation strategies (non-invasive ventilation (NIV) or high-flow nasal oxygen therapy (HFNO). Eighty-six (34.7%) received invasive mechanical ventilation without vvECMO. In total, 83 of 248 patients (33.5%) eventually received vvECMO. Patients suitable for vvECMO were fulfilling ECMO eligibility criteria of the EOLIA trial (10), while patients with serious comorbidities (e.g. advanced cardiac, respiratory, or liver failure, metastatic cancer and hematological malignancies) or patients older than 65 years (exemptions were made according to biological age) were excluded. All ECMO patients were part of the prospective DIVI COVID ECMO registry. The Ethics Committee at Würzburg University Hospital (Ethik-Kommission der Universität Würzburg 131-20) in addition to local ethics committees in centers approved the study protocol. Informed consent was waived for the anonymous data analysis.

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Eighteen of these patients qualified for awake-ECMO in the study period, since they were admitted awake, fully oriented and able to provide informed consent to the procedure during the study period (Figure 1A). Awake-ECMO patients were 55±13 years, with a body mass index (BMI) of 30.1±6.3 kg/m². Immediately prior to ECMO initiation, P_aO_2/F_iO_2 ratio at a PEEP of \geq 5 cmH₂O was 64.0±7.3 mmHg. Awake patients had a high respiratory rate (median 28.3±6.3 min⁻¹) and low recruitability prior to cannulation. All awake-ECMO patients continued non-invasive oxygen delivery via HFNO or NIV during ECMO treatment. Average demand on HFNO was 50±9 L/min, average inspiratory oxygen fraction 75±18%). Mean PEEP on mask or helmet non-invasive ventilation was 8.4±1.9 cmH₂O, average pressure support 11.1±5.0 cmH₂O and average inspiratory oxygen fraction on NIV 0.74±0.17. ECMO and ventilator support were adjusted at least every three hours according to blood gas analysis and patients' current respiratory effort. The following complications occurred in awake-ECMO patients: pulmonary superinfections (11/18, 61%), septic shock in 11/18 (61%), tension pneumothorax (3/18, 17%) and intracranial bleeding (1/18, 6%). Initially, all patients were devoid of sedatives and hence remained awake on participating wards. Patients were able to communicate with ICU personnel and able to express symptoms. Except for two patients who were able to stand and walk in the ICU, mobilization was limited within the bed or to the side of the bed in all other cases.

Importantly, 14 of 18 patients (78%) were intubated during intensive care therapy. Main reasons for switching from awake- to IMV-ECMO were delirium, patients' explicit wish to be sedated, tension pneumothorax with compromised airway, major bleeding or failure to oxygenate despite high ECMO blood flows. Awake-ECMO patients requiring delayed intubation had worse survival rates compared to the overall cohort (9/14, 64% vs. 50% in the overall cohort), as intubation was performed mainly due to complications. Subgroup analysis revealed that patients in the awake-ECMO group who managed to avoid intubation had lower BMI (25.2±2.4 vs 32.0±6.4 kg/m², p=0.005) and were cannulated sooner following admission to ICU for respiratory failure (mean time from admission to cannulation 81±21 hours vs. 192±167 hours, p=0.036). Average time on awake-ECMO was 320±252 hours.

Awake-ECMO patients were compared to a 1:1 propensity-score-matched control group receiving conventional management with vvECMO and IMV. Patients were matched according to ARDS severity (P_aO_2/F_iO_2 ratio at a PEEP of \geq 5 cmH₂O), age, BMI and left ventricular ejection fraction on admission (**Table I**). We did not detect significant differences in the occurrence of complications between groups. Overall time on vv-ECMO (independent of awake or sedated) was very well comparable between the two groups (583±478 hours for awake ECMO vs. 518±392 hours for control, p=0.66). ICU mortality for both the awake ECMO group and the matched control group (9 of 18, p=0.99; **Figure 1B**) was 50% while the overall mortality of COVID-19 patients treated non-awake with vvECMO in the study period was 53.8%.

The main findings of this study are: i) a high rate of patients receiving awake-ECMO in COVID-19 was finally intubated, ii) those subsequently intubated seem to have a higher mortality compared to CARDS patients managed conventionally with IMV and vvECMO.

Despite theoretical advantages of awake-ECMO with regard to gas exchange, respiratory effort and mobilization, endotracheal intubation could not be prevented in

most patients. Apart from acute complications (e.g. relevant bleeding or pneumothorax), bacterial superinfections, sepsis and disease progression finally led to respiratory exhaustion despite combined treatment with vvECMO and NIV.

Our study has limitations that need to be addressed: first, cohort size is relatively small, hence any conclusions on safety and complication rates of awake-ECMO for CARDS are uncertain. Second, we chose to compare the efficacy of awake-ECMO for COVID-19 to a cohort of patients being supported by both IMV and ECMO. Patients endotracheally intubated and managed without ECMO after failing noninvasive respiratory support might be in fact more suitable as a control group for awake-ECMO patients. However, a well-matched group might be difficult to define, as COVID-19 is a complex disease with variable clinical courses. Intubated and mechanically ventilated patients with COVID-19 that did not qualify for ECMO had a very high mortality rate (11).

In conclusion, the results so far don't favor an awake-ECMO approach for CARDS over conventional ECMO management, as most patients intubated after failing awake-ECMO appeared to have worse clinical outcome compared to the control group.

Thus, we cannot recommend an awake-ECMO approach for severe COVID-19 outside of clinical trials unless it were the explicit wish of the patient not to be intubated (9). Trials on the utilization and potential benefit of awake-ECMO will need to carefully identify patients suitable for an awake-ECMO approach and distinguish those patients with high chances to avoid IMV. Novel and additional strategies might be necessary to improve the success rate of awake-ECMO in CARDS patients.

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Time on mechanical ventilation [h] cannulation ejection fraction on admission **Outcome/ Mortality** Time admission to P/F-Ratio [mmHg] Serum creatinine [mg/dl] Cause of death Leftventricular cannulation / האז ההזההניהו Comorbidities Time on vv-ECMO (h) BMI [kg/m²] intubation? Age [years] Reason for Secondary intubation ę Type Sex **Control cohort** 55 28 65 96 3.7 >60% AHT; deep venous thrombosis 192 162 1 m fem-jug alive AHT; COPD; liver insufficiency; 2 46 26 64 12 2.2 >60% fem-jug 148 120 alive m immunosuppression 61 27 74 12 0.5 >60% AHT; S.P. sigma resection DLC 31F 2040 1704 alive 3 m 63 32 80 96 1.4 >60% AHT; hyperuricemia DLC 31F 1488 696 alive 4 m 5 m 48 34 81 96 0.8 >60% AHT fem-fem / fem-fem-jug 1344 1200 dead Septic shock 53 AHT 432 264 6 m 42 76 72 1.0 >60% fem-jug alive 39 12 AHT; DM Type II; S.P. astrocytoma 1032 ICB 7 m 23 69 1.0 >60% fem-jug 408 dead 69 35 80 120 >60% Rheumatoid arthritis; AHT; DM Type II 816 576 Ischemic colitis; DIC 8 1.1 fem-jug dead m 54 26 62 12 0.7 >60% fem-jug 360 336 dead MOF 9 m 69 48 AHT; CKD 720 10 f 29 62 0.8 >60% fem-jug 528 alive 54 28 55 192 2.5 >60% fem-jug 864 600 alive 11 m 12 m 30 29 60 12 1.1 >60% fem-jug 216 96 alive 67 72 2.9 >60% AHT; Atrial fibrillation; CKD 912 288 MOF 13 m 28 50 fem-jug dead 432 dead 68 35 70 24 2.4 >60% AHT; DM Type II fem-jug 408 MOF 14 m AHT 600 MOF 15 m 57 25 78 216 0.6 >60% fem-jug 480 dead 65 26 85 192 1.3 >60% AHT; DM Type II Fem-jug 648 336 alive 16 m 17 m 56 31 63 336 0.9 >60% fem-jug 672 660 dead Septic shock

Table I – Basic characteristics, clinical course and outcome of study populations

18	m	61	33	55	12	4.0	>60%	COPD;	fem-jug	480	456			dead	MOF
Σ	m	56.4 ± 10.7	29.8 ± 4.7	68.3 ± 10.3	91 ± 90	1.8 ± 1.2	>60%		fem-jug (15) / DLC (2) / fem-fem (1)	744 ± 492	518 ± 392			50% (9/18)	
									Awake cohort						
1	m	54	29	65	88	0.9	>60%	COPD;	fem-jug	144	240	yes	Hypox- emia	alive	
2	m	41	27	68	429	1.1	>60%	COPD; Rheumatoid arthritis; CKD;	fem-jug	192	600	yes	Hypox- emia	alive	
3	m	56	25	61	24	1.0	>60%		fem-jug	408	744	yes	Airway protect- ion	alive	
4	m	34	40	58	12	1.1	>60%	CKD; Epilepsy; Borderline personality disorder	fem-jug	768	816	yes	Patient's wish	dead	ICB / septic shock
5	m	62	44	71	48	0.9	>60%	AHT; DM Type II;	fem-jug	1176	1872	yes	Septic shock	Alive	
6	m	72	26	80	96	0.7	>60%	Coronary artery disease; Atrial fibrillation; AHT	DLC 31F	144	408	yes	Septic shock	alive	Septic shock
7	m	62	36	74	120	0.6	>60%	DM Type II	fem-jug	288	1008	yes	Septic shock	dead	Septic shock, bleeding
8	m	61	27	63	72	1.6	>60%		DLC 31F	0	96	no		alive	
9	f	18	32	65	264	0.7	>60%	AHT; DM Type II	fem-jug	576	840	yes	Patient's wish	dead	MOF
10	f	72	28	58	96	1.0	>60%	AHT	fem-jug	288	360	yes	Airway protection	dead	MOF
11	m	67	25	52	96	0.8	>60%	AHT; Rheumatoid arthritis	DLC 27F	0	216	no		alive	
12	m	60	26	54	408	1.5	>60%	COPD; DM Type II; CKD; AHT; VTE	DLC 27F	288	552	yes	Patient's wish	dead	MOF
13	m	67	35	61	456	1.3	>60%		fem-jug	984	1416	Yes	Airway protection	dead	Septic shock
14	m	51	28	61	24	0.7	>60%		Fem-jug	48	504	yes	Septic shock	dead	Septic shock
15	m	52	22	74	96	0.6	>60%	AHT	Fem-fem	0	120	no		alive	
16	m	54	40	63	336	0.8	>60%	AHT	fem-jug	120	144	yes	Septic shock	dead	MOF
17	m	52	24	65	48	1.0	>60%		fem-jug	0	144	no		alive	
18	m	55	28	57	192	0.8	>60%	Coronary artery disease; AHT; DM Type II	fem-jug	36	408	yes	Hypox- emia	dead	MOF

$\sum m \frac{55.0}{\pm 13.4} \frac{30.1}{\pm 6.3} \frac{64.0}{7.3} \frac{161}{149} \frac{0.9 \pm}{0.3} > 60\%$	yes Fem-jug (13) / DLC (4) / 390 ± 583 ± (13/18) 50% fem-fem (1) 357 478 /no (9/18) (5/18)
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Abbreviations: AHT = arterial hypertension / BMI = body mass index / CKD = chronic kidney disease / COPD = chronic obstructive pulmonary disease / DIC = Diffuse intravascular coagulation / DLC Double lumen cannula DM = diabetes mellitus / f = female / F = French / fem-jug = femoral-jugular / fem-fem = femoro-femoral / ICB = Intracerebral hemorrhage / ICU = intensive care Unit / / m = male / MOF = Multiorgan failure / P/F-Ratio = arterial oxygen partial pressure to inspiratory oxygen fraction ratio / S.P. = status post / vv-ECMO = veno-venous ECMO

Figure Legend

Figure 1A: Consort Diagram of Patients included in the final analysis.

Figure 1B: Kaplan-Meier estimate of survival for patients with CARDS managed awake on ECMO or conventionally (including intubation and mechanical ventilation). Kaplan-Meier-functions were plotted with SPSS version 26.0.0.0 and survival between both groups was compared using log-rank test.

Declarations

Ethics approval and consent to participate

Informed consent for the initiation of ECMO or awake-ECMO as part of intensive care measures for severe COVID-19 was obtained by the patient or legal representative.

ECMO patients were included in a prospective registry study (that has been approved by the ethics committee of the University of Würzburg (Ethik-Kommission der Universität Würzburg 131-20), the institutional review board of the board of physicians of the Federal State of Hessen (Ethik-Kommission bei der Landesärztekammer Hessen 2020-2135-AF and 2020-1653-zvBO, for the sites Kassel and Offenbach, respectively), the institutional review board of the board of physicians of the Federal State of Saarland (Ethikkommission der Ärztekammer des Saarlandes 208/20) and the Ethical committee of Hannover Medical School (Ethikkommission der Medizinischen Hochschule Hannover 9411_BO_K_2020). Informed consent for the analysis of data was waived by the institutional review board due to the anonymous and retrospective analysis of data.

Consent for Publication

Not applicable

Availability of data and materials

Data can be provided on request addressed to the corresponding author. All data sharing statements are subject to conformity with German data protection legislation and rules (Datenschutzgrundverordnung - DGSVO).

Competing interests

R.B. received funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Novartis, CSL Behring, German Federal Ministry of Education and Research (BMBF) Competence Network, Sander Stiftung, Dr Rolf M. Schwiete Foundation, German Cancer

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help (Krebshilfe) and Mukoviszidose e.V. All other authors have no conflicts of interest to declare.

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Author's Contribution

P.M.L., R.M.M., C.R. and S.M. drafted the study. C.R., H.M., P.M.L. and S.M. oversaw collection, review, and/or analysis of the data; C.R., P.M.L. and S.M. drafted the manuscript, H.M., R.N., C.L., D.G.-S., R.B., G.D., P.M., A.C., C.K., P.M.L. and R.M.M. revised the manuscript for important intellectual content. P.M.L. takes responsibility for the integrity of the work as a whole, from inception to published article. All authors have seen and approved the final version of the manuscript.

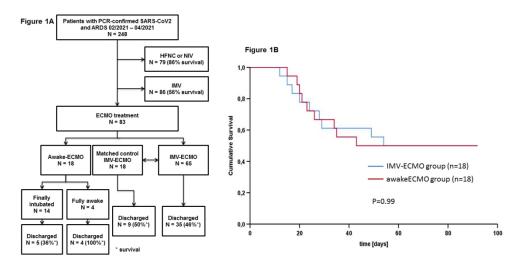




Figure 1B: Kaplan-Meier estimate of survival for patients with CARDS managed awake on ECMO or conventionally (including intubation and mechanical ventilation). Kaplan-Meier-functions were plotted with SPSS version 26.0.0.0 and survival between both groups was compared using log-rank test.

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