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## Awake Extracorporeal Membrane Oxygenation for COVID-19–induced Acute Respiratory Distress Syndrome

*To the Editor*:

The outcome of patients with coronavirus disease (COVID-19) treated in ICUs is unsatisfying (1). Venovenous extracorporeal membrane oxygenation (vvECMO) can serve as a rescue strategy when patients deteriorate during invasive ventilation (2, 3). Using 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, self-inflicted lung injury (7). Reports on awake-ECMO for COVID-19 are currently limited to case reports (8, 9).

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. Patients undergoing ECMO were included in the prospective Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI) COVID ECMO registry, which 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 because of the anonymous and retrospective analysis of data.

We report 18 adult patients with real-time RT-PCR–confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)



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Author Contributions: 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.

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]).

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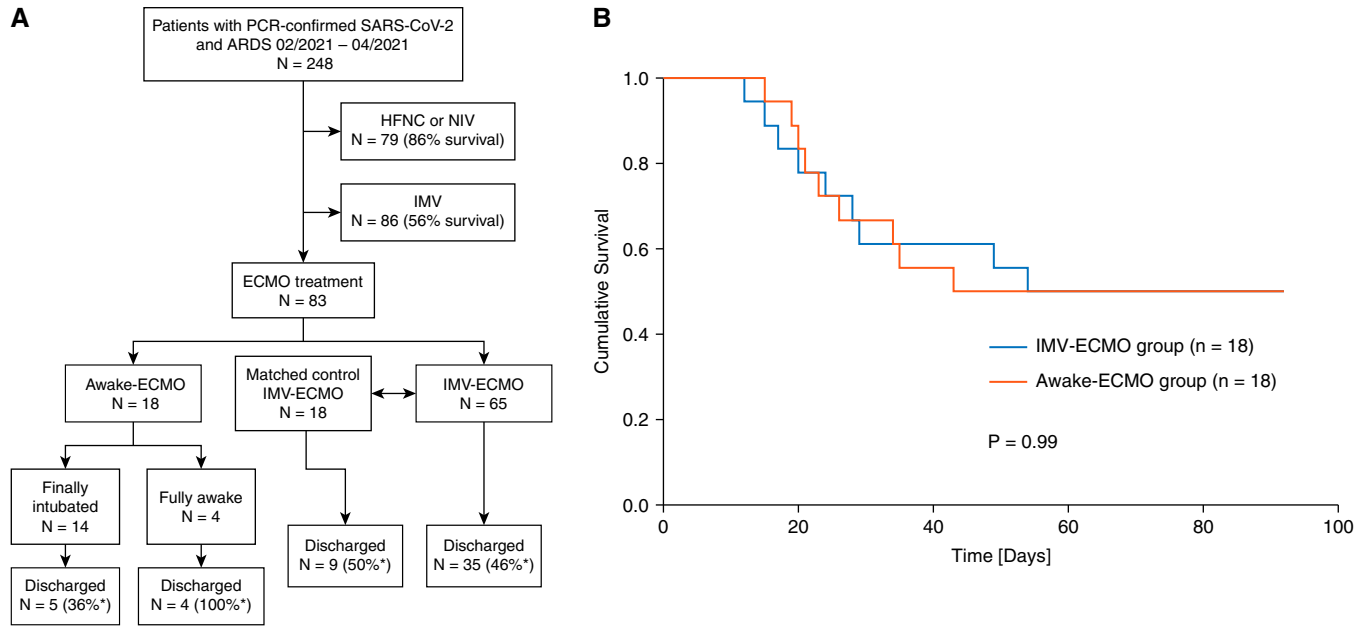


**Figure 1.** (*A*) Consort diagram of patients included in the final analysis. (*B*) Kaplan-Meier estimate of survival for patients with COVID-19–acute respiratory distress syndrome managed awake on ECMO or conventionally (including intubation and mechanical ventilation). Kaplan-Meier functions were plotted with SPSS version 26.0.0.0, and survival between both groups was compared using log-rank test. *indicates survival. ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; HFNO = high-flow nasal oxygen; IMV = invasive mechanical ventilation; NIV = noninvasive ventilation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

infection and hypoxemic COVID-19 acute respiratory distress syndrome (CARDS) supported awake on vvECMO in four German tertiary care ICUs from February 1 to April 30, 2021. During the study period, a total of 248 patients with COVID-19 were hospitalized on these wards. Seventy-nine of these (31.9%) were supported with noninvasive oxygenation strategies (noninvasive ventilation [NIV] or high-flow nasal oxygen [HFNO] therapy). Eighty-six (34.7%) received invasive mechanical ventilation (IMV) without vvECMO. In total, 83 of 248 patients (33.5%) eventually received vvECMO. Patients suitable for vvECMO were fulfilling ECMO eligibility criteria of the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial (10), whereas 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. Eighteen of these patients qualified for awake-ECMO in the study period, as 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 of age, with a body mass index (BMI) of 30.1 ± 6.3 kg/m$^2$. Immediately before ECMO initiation, $Pa_{O_2}/Fi_{O_2}$ ratio at a positive end-expiratory pressure (PEEP) of at least 5 cm $H_2O$ was 64.0 ± 7.3 mm Hg. Awake patients had a high respiratory rate (median, 28.3 ± 6.3 min$^{-1}$) and low recruitability before cannulation. All awake-ECMO patients continued noninvasive 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 NIV was 8.4 ± 1.9 cm $H_2O$, average pressure support 11.1 ± 5.0 cm $H_2O$, and average inspiratory oxygen fraction on NIV 0.74 ± 0.17. ECMO and ventilator support were adjusted at least every 3 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 (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 with the overall cohort (9/14, 64% vs. 50% in the overall cohort), as intubation was performed mainly because of 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/m$^2$, $P = 0.005$) and were cannulated sooner after admission to the ICU for respiratory failure (mean time from admission to cannulation, 81 ± 21 h vs. 192 ± 167 h, $P = 0.036$). Average time on awake-ECMO was 320 ± 252 hours.

Awake-ECMO patients were compared with a 1:1 propensity score–matched control group receiving conventional management with vvECMO and IMV. Patients were matched according to ARDS severity ($Pa_{O_2}/Fi_{O_2}$ ratio at a PEEP of ⩾5 cm $H_2O$), age, BMI, and left ventricular ejection fraction on admission (Table 1). We did not detect significant differences in the occurrence of complications

**Table 1.** Basic Characteristics, Clinical Course, and Outcome of Study Populations

| | Sex | Age (*yr*) | BMI ($kg/m^2$) | P/F Ratio (*mm Hg*) | Time from Admission to Cannulation/ Intubation (*h*) | Serum Creatinine (*mg/dl*) | Left Ventricular Ejection Fraction on Admission | Comorbidities | Type of Cannulation | Time on Mechanical Ventilation (*h*) | Time on vvECMO (*h*) | Secondary Intubation? | Reason for Intubation | Outcome/ Mortality | Cause of Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control cohort | | | | | | | | | | | | | | | |
| 1 | M | 55 | 28 | 65 | 96 | 3.7 | >60% | AHT; deep venous thrombosis | Fem-jug | 192 | 162 | | | Alive | |
| 2 | M | 46 | 26 | 64 | 12 | 2.2 | >60% | AHT; COPD; liver insufficiency; immunosuppression | Fem-jug | 148 | 120 | | | Alive | |
| 3 | M | 61 | 27 | 74 | 12 | 0.5 | >60% | AHT; S.P. sigma resection | DLC 31F | 2,040 | 1,704 | | | Alive | |
| 4 | M | 63 | 32 | 80 | 96 | 1.4 | >60% | AHT; hyperuricemia | DLC 31F | 1,488 | 696 | | | Alive | |
| 5 | M | 48 | 34 | 81 | 96 | 0.8 | >60% | AHT | Fem-fem/fem-fem-jug | 1,344 | 1,200 | | | Dead | Septic shock |
| 6 | M | 53 | 42 | 76 | 72 | 1.0 | >60% | AHT | Fem-jug | 432 | 264 | | | Alive | |
| 7 | M | 39 | 23 | 69 | 12 | 1.0 | >60% | AHT; DM type II; S.P. astrocytoma | Fem-jug | 1,032 | 408 | | | Dead | ICB |
| 8 | M | 69 | 35 | 80 | 120 | 1.1 | >60% | Rheumatoid arthritis; AHT; DM type II | Fem-jug | 816 | 576 | | | Dead | Ischemic colitis; DIC |
| 9 | M | 54 | 26 | 62 | 12 | 0.7 | >60% | | Fem-jug | 360 | 336 | | | Dead | MOF |
| 10 | F | 69 | 29 | 62 | 48 | 0.8 | >60% | AHT; CKD | Fem-jug | 720 | 528 | | | Alive | |
| 11 | M | 54 | 28 | 55 | 192 | 2.5 | >60% | | Fem-jug | 864 | 600 | | | Alive | |
| 12 | M | 30 | 29 | 60 | 12 | 1.1 | >60% | | Fem-jug | 216 | 96 | | | Alive | |
| 13 | M | 67 | 28 | 50 | 72 | 2.9 | >60% | AHT; atrial fibrillation; CKD | Fem-jug | 912 | 288 | | | Dead | MOF |
| 14 | M | 68 | 35 | 70 | 24 | 2.4 | >60% | AHT; DM type II | Fem-jug | 432 | 408 | | | Dead | MOF |
| 15 | M | 57 | 25 | 78 | 216 | 0.6 | >60% | AHT | Fem-jug | 600 | 480 | | | Dead | MOF |
| 16 | M | 65 | 26 | 85 | 192 | 1.3 | >60% | AHT; DM type II | Fem-jug | 648 | 336 | | | Alive | |
| 17 | M | 56 | 31 | 63 | 336 | 0.9 | >60% | | Fem-jug | 672 | 660 | | | Dead | Septic shock |
| 18 | M | 61 | 33 | 55 | 12 | 4.0 | >60% | COPD | Fem-jug | 480 | 456 | | | Dead | MOF |
| ∑ | 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 | Hypoxemia | Alive | |
| 2 | M | 41 | 27 | 68 | 429 | 1.1 | >60% | COPD; rheumatoid arthritis; CKD | Fem-jug | 192 | 600 | Yes | Hypoxemia | Alive | |
| 3 | M | 56 | 25 | 61 | 24 | 1.0 | >60% | | Fem-jug | 408 | 744 | Yes | Airway protection | 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 | 1,176 | 1,872 | 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 | 1,008 | 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 |

(*Continued*)

**Table 1.** (*Continued*)

| | Sex | Age (*yr*) | BMI (*kg/m²*) | P/F Ratio (*mm Hg*) | Time from Admission to Cannulation/ Intubation (*h*) | Serum Creatinine (*mg/dl*) | Left Ventricular Ejection Fraction on Admission | Comorbidities | Type of Cannulation | Time on Mechanical Ventilation (*h*) | Time on vvECMO (*h*) | Secondary Intubation? | Reason for Intubation | Outcome/ Mortality | Cause of Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | M | 67 | 35 | 61 | 456 | 1.3 | >60% | | Fem-jug | 984 | 1,416 | 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 | Hypoxemia | Dead | MOF |
| ∑ | M | 55.0 ± 13.4 | 30.1 ± 6.3 | 64.0 ± 7.3 | 161 ± 149 | 0.9 ± 0.3 | >60% | | Fem-jug (13)/ DLC (4)/fem-fem (1) | 390 ± 357 | 583 ± 478 | Yes (13/18)/ no (5/18) | | 50% (9/18) | |

*Definition of 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 = French; fem-fem = femorofemoral; fem-jug = femoral-jugular; ICB = intracerebral hemorrhage; MOF = multiorgan failure; P/F ratio = arterial oxygen partial pressure to inspiratory oxygen fraction ratio; S.P. = status post; VTE = venous thromboembolism; vvECMO = venovenous extracorporeal membrane oxygenation.

between groups. Overall time on vvECMO (independent of awake or sedated) was comparable between the two groups (583 ± 478 h for awake-ECMO vs. 518 ± 392 h for control, $P = 0.66$). ICU mortality for both the awake-ECMO group and the matched control group (9/18, $P = 0.99$) (Figure 1B) was 50%, and the overall mortality of patients with COVID-19 treated nonawake with vvECMO in the study period was 53.8%.

The main findings of this study are *1*) a high rate of patients receiving awake-ECMO in COVID-19 were finally intubated; and *2*) those subsequently intubated seem to have a higher mortality than patients with CARDS 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 who did not qualify for ECMO had a very high mortality rate (11).

In conclusion, the results so far do not 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 with 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 use 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 patients with CARDS. ■

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## Remote 6-Minute-Walk Testing in Patients with Pulmonary Hypertension: A Pilot Study

*To the Editor*:

Exercise limitation is a hallmark of pulmonary hypertension (PH). The 6-minute-walk test (6MWT) is a self-paced test of exercise capacity used to evaluate risk and therapeutic response and as a trial endpoint in pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) (1). The 6MWT is standardly administered only in clinical or research settings with strict protocols (2). Because of the increase in telemedicine and remote care during the coronavirus disease (COVID-19) pandemic, we sought to determine the feasibility, safety, and

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