Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Physical Therapy and Sedation While on Extracorporeal Membrane Oxygenation for COVID-19–Associated Acute Respiratory Distress Syndrome

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Objectives: This study aimed to determine whether patients on extracorporeal membrane oxygenation (ECMO) with coronavirus disease 2019 (COVID-19) achieved lower rates of physical therapy participation and required more sedation than those on ECMO without COVID-19.
Design: Retrospective, observational, matched-cohort study.
Setting: Bicenter academic quaternary medical centers.
Participants: All adults on ECMO for severe COVID-19-associated acute respiratory distress syndrome (ARDS) during 2020 and matched (matched 1:1 based on age ± 15 years and medical center) adults on ECMO for ARDS not associated with COVID-19.
Interventions: Observational only.
Measurements and Main Results: Measurements were collected retrospectively during the first 20 days of ECMO support and included daily levels of physical therapy activity, number of daily sedation infusions and doses, and level of sedation and agitation (Richmond Agitation and Sedation Score). During the first 20 days of ECMO support, the 22 patients who were on ECMO for COVID-19–associated ARDS achieved a similar proportion of days with active physical therapy participation while on ECMO compared to matched patients on ECMO for non-COVID-19 ARDS (22.5% *v* 7.5%, respectively; p value 0.43), a similar proportion of days with Richmond Agitation and Sedation Score ≥-2 while on ECMO (47.5% *v* 27.5%, respectively; p value 0.065), and a similar proportion of days with chemical paralysis while on ECMO (8.4% *v* 18.0%, respectively; p value 0.35).
Conclusions: The results of this matched cohort study supported that sedation requirements were not dramatically greater and did not significantly limit early physical therapy for patients who had COVID-19–associated ARDS and were on venovenous extracorporeal membrane oxygenation (VV-ECMO) versus those without COVID-19–associated ARDS who were on VV-ECMO.

Key Words: extracorporeal membrane oxygenation; ECMO; adult; COVID-19; sedation; physical therapy

SINCE THE APPEARANCE of patients with severe coronavirus disease 2019 (COVID-19) in intensive care units across the world in 2020, clinicians and researchers have been reporting their experiences caring for these unique patients. An area of particular interest has been the sedation requirements of this cohort of patients.

Before COVID-19, sedation and mobilization of adults on extracorporeal membrane oxygenation (ECMO) were described and noted generally high sedation requirements.[1-3]

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In a study by deBacker et al. of patients on ECMO for respiratory failure between 2012 and 2015, most patients were deeply sedated for the first six days of ECMO, after which 71% of patients were eventually awake enough to participate in physical therapy.[4] Early mobility and physical therapy in patients on ECMO have been shown to be safe and potentially associated with decreased ICU mortality.[5,6]

Early reports from Hanidziar et al. noted that many patients with COVID-19 had "unusually high sedation requirements," and attributed this to younger average age, high respiratory drive, and intense inflammation associated with COVID-19.[7] A subsequent case series of 24 patients requiring mechanical ventilation with COVID-19 demonstrated that this cohort required substantially more sedation than historic controls without COVID-19.[8] As the cumulative experience with COVID-19 has expanded, some have suggested that a new approach to multimodal sedation for patients with COVID-19 may be required.[9]

Based on published reports and anecdotes, the sedation requirements of patients with COVID-19 on ECMO remains an area of active interest. A related knowledge gap that persists is whether a difference in degree of sedation also may affect patients' ability to participate in physical therapy. In this study, the authors sought to compare the sedation requirements and ability to participate actively in physical therapy in adult patients on ECMO for respiratory failure with COVID-19 versus those without COVID-19. The authors hypothesized that patients with COVID-19 on ECMO would require more sedation and achieve active physical therapy less frequently than patients with non-COVID-19 respiratory failure on ECMO.

Methods

After receiving institutional review board approval from both study sites (IRB 20-013094), the existing ECMO database was queried to compile a complete list of all adult patients on venovenous extracorporeal membrane oxygenation (VV-ECMO) for ARDS between January 1, 2019, and December 31, 2020. From this list, each patient on VV-ECMO for COVID-associated ARDS was matched 1:1 to a patient without COVID-associated ARDS; matching was based on study site and age (±15 years). A detailed retrospective chart review was completed to record demographic variables and then the complete set of study variables of interest, which all had been determined a priori.

From a clinical perspective, the study institutions did not use a strict sedation algorithm. Choice of sedatives and sedation goals was at the discretion of the consultant physician. Light levels of sedation (Richmond Agitation and Sedation Score [RASS] −1 to 0) were targeted whenever possible. In very general terms, clinicians aimed to titrate sedatives to achieve a safe balance of patient comfort, lack of agitation, ability to participate in physical therapy, and facilitation of lung-protective ventilation. This practice is similar to that recommended in the Society of Critical Care Medicine's Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation, Delirium, Immobility, and Sleep.[10] The ICUs in the study institutions also have imbedded physical therapist teams, which help facilitate early physical therapy consultation.

The primary study variables pertaining to sedation medications, Richmond Analgesia and Sedation Score (RASS), and physical therapy activity were recorded for each day that each patient was on ECMO. The RASS was documented routinely by the trained nursing staff while in the intensive care unit and the RASS recorded at 12:00 PM each day was collected and recorded for this study.[11] The "number of sedation infusions" was determined at 12:00 PM each day; sedation infusions included any of the following: propofol, midazolam, lorazepam, dexmedetomidine, ketamine, fentanyl, and hydromorphone. The use of any other sedation infusions was extremely rare at the study institutions. The predominant sedative infusions used in the study population were propofol, ketamine, and dexmedetomidine; total daily doses (including infusions and boluses) of propofol, ketamine, and dexmedetomidine were recorded. Opioid oral morphine equivalents (OMEs) were calculated based on standard opioid conversion and included all intravenous and enteral opioids administered.[12,13] Chemical paralysis use was defined by use of a chemical paralytic infusion at any point during the 24-hour period; paralytic boluses were not recorded in this study, as boluses typically were used only to facilitate procedures. Daily physical therapy was documented by either the ICU nurse or physical therapist. Passive physical therapy (PT) was defined as range-of-motion exercises performed by the care team without volitional effort exerted by the patient. Active physical therapy was movement or exercise during which the patient participated and exerted effort. The documentation reviewed in a retrospective manner did not have sufficient detail to accurately assign levels of activity described in the well-established ICU mobility score; therefore, this study used a simple ordinal score from 0-to-3 points.[14] For the purposes of this study, PT was recorded on a scale of 0 to 3; 0 = none, 1 = passive PT only, 2 = active PT, and 3 = ambulation. Documentation differentiating levels 0 and 1 often were unclear, so these two levels (0 and 1) were combined for practical purposes and recorded as "0-1." For each ECMO day, the maximum physical therapy level was recorded in the study database.

The primary outcome, which was determined a priori, was the proportion of days on ECMO with PT level ≥2 (active PT or ambulation). The statistical power analysis for this primary outcome determined that a difference in proportions of 33%, with a study power of 80% and $\alpha < 0.05$, would require fewer than 40 participants in each study group. Unfortunately, from a statistical standpoint, but fortunate from a clinical standpoint, over the entire study period the authors had fewer than 40 participants requiring ECMO for COVID-19.

Secondary endpoints investigated in this study were proportion of ECMO days with any paralytic infusion (excluding any paralytic boluses), total sedation dosing per ECMO day (propofol, ketamine, dexmedetomidine, and opioids; including infusions and boluses), and daily level of sedation while on ECMO (reported as RASS). Primary and secondary endpoint comparisons excluded data from ECMO day zero (day of ECMO initiation), because this period could be biased by interventions (including sedative and paralytic dosing), which were required during maximal ventilator support immediately prior to and during ECMO cannulation.

The data were analyzed in a standard approach. Descriptive statistics of categorical data were reported as numbers and percentages. Statistical comparisons of categorical data were performed using Fisher exact test. Descriptive statistics of non-normally distributed continuous data were reported as median and interquartile range. Statistical comparisons of non-normally distributed continuous data were performed using the Mann-Whitney U test. For all analyses, a p value < 0.05 was considered statistically significant. All statistical tests were performed using JMP Pro version 14.1.0 (SAS Institute Inc, Cary, NC).

Results

During the study period between January 1, 2019, and December 31, 2020 at the participating study institutions, a total of 22 participants required VV-ECMO for COVID-19−associated ARDS and 22 site- and age-matched controls required VV-ECMO for non-COVID-19-associated ARDS. Demographics for these two groups are summarized in Table 1.

Table 1
Demographics

Demographics	non-COVID	COVID+	p Value
Total participants	22	22	
Age, median (IQR)	50 (39.5-56)	50.5 (43-56.3)	0.67
Male, n (%)	16 (72.7)	16 (72.7)	1
Weight (kg), median (IQR)	79.7 (70.8-106.6)	99.6 (78.6-113.8)	0.14
BMI (kg/m^2), median (IQR)	28.7 (26.1-34.8)	31.2 (29.1-37.9)	0.087
Comorbidities			
Hypertension, n (%)	7 (31.8)	9 (40.9)	0.75
Diabetes mellitus, n (%)	3 (13.6)	5 (22.7)	0.69
Chronic kidney disease, n (%)	2 (9.1)	3 (13.6)	1
Coronary artery disease, n (%)	1 (4.5)	2 (9.1)	1
COPD, n (%)	4 (18.2)	0 (0)	0.11
Cause of ARDS			<0.001
COVID-19, n (%)	0 (0)	22 (100)	
Influenza, n (%)	9 (40.9)	0 (0	
Bacterial pneumonia, n (%)	6 (27.3)	0 (0)	
Other,* n (%)	7 (31.8)	0 (0)	
ECMO initiation year, (n, %)			
2019	13 (59.1)	0 (0)	<0.001
2020	9 (40.9)	22 (100)	
Venovenous configuration, n (%)	22 (100)	22 (100)	1
Femoral-IJ, n (%)	19 (86.4)	20 (90.9)	0.60
IJ dual-lumen cannula, n (%)	1 (4.5)	0 (0)	
Femoral-femoral, n (%)	2 (9.1)	2 (9.1)	
ECMO duration (h), median (IQR)	480 (184-625)	618 (306-990)	0.19
Survival to hospital discharge, n (%)	15 (68.2)	16 (72.7)	1
Tracheostomy on ECMO, n (%)	12 (54.5)	12 (54.5)	1

NOTE. Continuous variables analyzed with Mann-Whitney U test. Categorical variables analyzed with Fisher exact test.
Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; COVID+, COVID-positive; non-COVID, non-COVID related respiratory failure; ECMO, extracorporeal membrane oxygenation; IJ, internal jugular vein; IQR, interquartile range.
* Other includes transfusion-related acute lung injury, trauma, sepsis, pancreatitis, unknown.

For the study's primary outcome, the proportion of ECMO days with PT level ≥2 (active PT and/or ambulation) was compared and outlined in Table 2. During the first 20 days of VV-ECMO, patients who were COVID-positive (COVID+) on ECMO achieved a PT level ≥2 on a median proportion of 58% of ECMO days, while patients with non−COVID-related respiratory failure on ECMO achieved a PT level ≥2 on a median proportion of 31% of ECMO days (p value 0.43).

For the secondary endpoints, the results of these comparisons are outlined in Table 2. During the first 20 days of VV-ECMO, the COVID+ ECMO group had a RASS ≥−2 on a median of 47.5% of ECMO days, compared to only a median of 27.5% of ECMO days in the non-COVID ECMO group (p value 0.065). During the first 20 days of VV-ECMO, the COVID+ ECMO group required chemical paralysis during a median of 8.4% of ECMO days, compared to 18.0% of days for the non-COVID ECMO group (p value 0.35). During the first 20 days of VV-ECMO, the COVID+ ECMO group required a median number of 2.5 sedative infusions per day

Table 2
Outcomes During First 20 ECMO Days

	COVID+ Group	non-COVID Group	p Value
Total patients who underwent ECMO	22	22	
Total ECMO patient days*	280	252	
Median proportion of ECMO days with PT level ≥2, median (IQR)	0.225 (0-0.58)	0.075 (0-0.31)	0.43
Median proportion of ECMO days with RASS ≥ -2, median (IQR)	0.475 (0.32-0.87)	0.275 (0-0.68)	0.065
Median proportion of ECMO days with paralytic infusion, median (IQR)	0.084 (0-0.22)	0.18 (0-0.31)	0.35
Median number of sedation infusions per day while on ECMO, median (IQR)	2.5 (1.0-3.0)	2.0 (1.0-3.0)	0.71
Total propofol dose (mg/kg/ECMO h), median (IQR)	0.77 (0.46-0.98) Range = 0-133.2	0.48 (0.34-0.84) Range = 0-194.1	0.37
Total ketamine dose (mg/kg/ECMO h), median (IQR)	0.002 (0.0-0.11) Range = 0-47.9	0.0 (0.0-0.23) Range = 0-30.1	0.22
Total dexmedetomidine dose (μg/kg/ECMO h), median (IQR)	0.32 (0.07-0.62) Range = 0-50.0	0.52 (0.11-0.86) Range = 0-75.1	0.35

NOTE. PT level ≥ 2 equals active PT and/or ambulation.
Abbreviations: COVID-19, coronavirus disease 2019; COVID+, COVID-positive; non-COVID, non-COVID related respiratory failure; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; PT, physical therapy; RASS, Richmond Agitation and Sedation Score.
* Only the first 20 days after ECMO initiation included. ECMO day 0 (day of ECMO initiation) excluded from these analyses.

while on ECMO, compared to a median number of 2.0 sedative infusions per day while on ECMO in the non-COVID ECMO group (p value 0.71). Total doses of the three primary sedative infusions used (propofol, ketamine, and dexmedetomidine) were not statistically significantly different between the COVID+ and non-COVID ECMO groups, and the results are detailed in Table 2.

Additional analyses of associations with successful achievement of active physical therapy (PT level ≥2) are presented in the Appendix. These analyses were not intended to specifically identify differences between patients who were COVID+ and those with non−COVID-related respiratory failure on ECMO. These comparisons revealed that there was no clear association between the proportion of ECMO days with PT ≥2 and survival to hospital discharge. Among participants who survived to hospital discharge, there was a non-statistically significant association between discharge destination and proportion of ECMO days with PT ≥ 2.

Further analysis of population data (combined data of participants in the COVID+ ECMO cohort versus participants in the non-COVID−related respiratory failure ECMO cohort) are presented in the Appendix. The population-level data revealed that during the first 30 days of ECMO support, patients in the COVID+ group received a similar number of sedative infusions and a similar number of total OME per day compared to those in the non-COVID group. Additionally, the proportion of ECMO days with an endotracheal tube in place was not statistically significantly different between the patients positive for COVID-19 on ECMO and those without COVID-19−associated respiratory failure on ECMO (0.59 *v* 0.56, respectively; p value 0.48), and is reported in the Appendix.

Discussion

Despite the hypothesis that patients on VV-ECMO for COVID-19−associated ARDS would require more sedation and, therefore, would be less participatory in PT, the data from this study did not support that hypothesis. In this study, the authors found that during the first 20 days of VV-ECMO, patients with COVID-19 achieved active PT participation on a similar proportion of ECMO days, required chemical paralysis on a similar proportion of days, and did not have a statistically significantly different level of sedation (proportion of days with RASS ≥ −2) compared to patients without COVID. Patients with COVID on VV-ECMO also did not have a significantly different median number of sedation infusions per day, total propofol dosing, total ketamine dosing, or total dexmedetomidine dosing while on VV-ECMO.

Although patients who were COVID+ and on VV-ECMO did not appear to have any significant differences in sedation requirements when comparing individual sedatives, does that mean they also did not have any significant difference in cumulative sedation requirements? There is no standardized "sedation equivalent" conversion available for intravenous sedatives (other than OME for opioids). A potential solution for this problem that could be considered would be processed encephalography (such as bispectral index monitoring). However, a bispectral index would measure level of alertness (which should be similar to what the authors already measured with RASS), and not a cumulative dose equivalent of all the simultaneous sedative infusions and opioids.

Another key limitation of the study presented here was the lack of protocolized sedation algorithms (or at least rigidly documented rationale for sedation dosing changes). This limitation is inherent to the retrospective observational design, but it introduces variability into the data and confounds the interpretation of the data. Due to this limitation, it is certainly possible that an unrecognized confounding factor may have influenced the choice of sedation medications and sedation level targets. An important data point that is absent from the patient records in this study is the rationale for changing sedation regimens and dosing. For example, was sedation increased due to agitation, delirium, subjective air hunger, excessive respiratory efforts, or something else? A significant proportion of patients with ARDS (approximately 50%) do not tolerate spontaneous breathing trials even while fully supported on ECMO, so in this study perhaps a large number of the patients also did not tolerate spontaneous breathing trials and, therefore, required more sedation to ensure lung-protective ventilation.[15] Regarding the risk of chance influencing the findings of this study, the use of primary and secondary endpoints chosen a priori substantially protected against this risk, but the limited statistical power (due to a relatively small number of participants with COVID-19) increased this risk.

The results of the study differed somewhat compared to the data reported by Hanidziar et al. and Kapp et al.[7,8] Both groups reported a substantially higher sedation requirement for patients with COVID-19. The reason for these differences may be due to any number of factors, but one factor that deserves mention is the timing and context of the data. The data reported by Hanidziar et al. and Kapp et al. came earlier during the pandemic when the authors' COVID-19 experience was more limited and ICU censuses were surging. Perhaps, with crisis mode staffing during early COVID-19 surges, there was a tendency to sedate patients more deeply to avoid any unplanned complications from agitation, such as self-extubation. Similarly, it is plausible that observer bias or a few notable outliers may have colored the authors' impressions, suggested an increased sedation requirement in patients with COVID-19, and prompted them to formulate the hypothesis for the current study. At least based on the range of total daily propofol, ketamine, and dexmedetomidine, there was no objective evidence of even a few outliers requiring significantly higher sedative doses in the COVID+ group. One additional potential confounder worth mentioning is that most of the included patients had at least one femoral ECMO cannula, which potentially could interfere with PT efforts. However, there was no significant difference in cannulation configurations between the COVID+ and non-COVID VV-ECMO groups.

All in all, the results of this matched cohort study of patients on ECMO suggested that the sedation requirements for patients with COVID-19−associated ARDS did not limit early PT compared with those on ECMO for non−COVID-19

ARDS. The results of this study did not support the hypothesis (nor did they definitely rule out the hypothesis) that patients with COVID-19–associated ARDS on VV-ECMO require increased sedatives to achieve an equivalent level of sedation. To bring more clarity to this question, a more standardized clinical approach to sedation regimens could help control some potential confounders.

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Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.06.030.

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