Propofol Safety in Anticoagulated and Nonanticoagulated Patients During Extracorporeal Membrane Oxygenation

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Sedation management during extracorporeal membrane oxygenation (ECMO) is a common challenge encountered by treating intensivists. Data about the safety of propofol use during ECMO has been contradictory. We aimed to investigate associated risks of propofol use on oxygenator lifespan and to explore the effect of propofol use on oxygenator membranes when therapeutic anticoagulation was omitted. Adult respiratory ECMO patients who received propofol were retrospectively compared with those who did not, and outcomes were assessed by means of duration of oxygenator functionality before requiring an exchange, and number of exchanges during propofol use and/or ECMO support. Out of the 63 patients included in the analysis, 46% received propofol during ECMO as part of sedation regimen. The use of propofol was not found to be associated with an increased incidence of oxygenator failure when compared with cohorts who did not receive propofol (21% propofol arm vs. 6% control, $p = 0.13$). When analyzed for anticoagulation omission effects, propofol did not increase the risk of oxygenator failure ($p = 0.63$). The only predictor that statistically predicted the risk of oxygenator failure was development of heparin-induced thrombocytopenia (HIT) during ECMO. The results of this study further support the previously reported safety of propofol utilization during respiratory ECMO even in the absence of anticoagulation. ASAIO Journal 2021; 67:201–207.

Key Words: sedation, propofol, ECMO, anticoagulation, oxygenator running time, oxygenator exchange

Extracorporeal membrane oxygenation (ECMO) is an artificial circulatory support that has enormously evolved over the last decade and become a vital option for the treatment of refractory cases of cardiac and/or respiratory failure.¹ Contrary to the cardiac ECMO support that has been used for decades as a bridge to heart transplantation, the utility of respiratory ECMO support became more evident only recently after the H1N1 pneumonia outbreak in 2009,²,³ with more than 21,000 cases reported using respiratory ECMO support by 2019.⁴ The management of patients on ECMO is usually complex, requiring different therapies not only targeting the underlying cause of cardiac and/or respiratory failure, but also for the prevention of various complications. Ensuring adequate sedation during ECMO support is extremely crucial, since patients usually have additional reasons necessitating deeper levels of sedation, such as severe hypoxemia or prevention of catastrophic events like self-de-cannulation.³ Numerous pharmacokinetic variations are commonly encountered in such populations, including increased drug volume of distribution and/or adsorption of different medications to the ECMO circuit.⁵,⁶ For instance, highly lipophilic drugs commonly employed in sedating critically ill patients have been well documented to adhere to different components of the circuit (cannulas and oxygenators) and thus result in increased dosing requirements to attain target analgesedation targets.⁹,¹⁰ Despite being one of the front-line sedatives commonly used in intensive care units (ICUs),¹¹ the use of propofol during ECMO has been limited and often avoided. Because of drug adsorption and subsequent higher dosage requirements, many clinicians fear the risk of developing propofol infusion syndrome (PRIS).¹² Furthermore, layering, agglutination, and subsequent oxygenator failure were previously documented with the use of intralipid emulsions during ECMO.¹³,¹⁴ Since propofol emulsion is identical to intralipid emulsion, risks were extrapolated from such studies, and the utilization of propofol was further restricted. This was demonstrated by an international survey conducted in collaboration with the Extracorporeal Life Support Organization (ELSO), which revealed infrequent propofol use (36% of respondents) as a sedating agent for patients requiring respiratory adult ECMO.¹⁵ Nevertheless, propofol use during ECMO has recently gained interest, especially with evolving reports of safety. This was initiated by an in-vitro analysis conducted in 2009, assessing the effects of different dosages of propofol on oxygenator performance, where researchers concluded minimal risks of propofol on the gas exchange abilities of the oxygenators.¹⁶ To replicate the results clinically, Hohlfelder et al.¹⁷ retrospectively reviewed the use of propofol across their ECMO population and confirmed the safety of propofol without associated risks of decreased circuit lifespan or impaired oxygenation. A similar conclusion was also reported by Lamm et al.,¹⁸ yet in their population, propofol was more predominantly used in cardiac ECMO support as opposed to respiratory support. Of note, in all the aforementioned studies, therapeutic anticoagulation...
was always maintained with the aim to suppress hemostatic activation and prevent thrombosis.\(^{19}\)

In Qatar, cardiac and pediatric ECMO services have been used for many years. However, a respiratory adult ECMO service was recently implemented in 2014. The choice of the sedative/analgesic agents during ECMO is usually based on the clinician’s preference. Unlike cardiac ECMO cases, several respiratory adult ECMO cases run without full anticoagulation for varying reasons. Owing to the inconsistent agreements and heterogeneity of the populations studied, we sought to investigate whether propofol use in adult respiratory ECMO patients was associated with an amplified risk of oxygenator failure. Furthermore, since a substantial number of our patients, unlike other cohorts, end up not receiving full anticoagulation, we aimed to explore the effect of propofol use on oxygenator lifespan when therapeutic anticoagulation is not feasible.

### Materials and Methods

This was a retrospective observational analysis conducted at Hamad General Hospital (HGH), the tertiary governmental hospital of Qatar.

A list of all patients who were placed on ECMO since the initiation of adult respiratory ECMO service (December 2014) until December 2017 was obtained from the department ECMO registry. To be included in the analysis, patients must have received respiratory ECMO (i.e., Veno-venous ECMO; VV-ECMO) support for at least 48 hours. Exclusion criteria included ECMO support for less than 48 hours or for cardiac indications (i.e., Veno-arterial ECMO [VA-ECMO] or ECMO-CPR [ECP]).

After running inclusion/exclusion criteria, pertinent information regarding all the remaining patients was collected and analyzed. Data collection included patient demographics, indication and duration of ECMO support, number of patients who required any circuit exchange while on ECMO, total number of circuit exchanges because of oxygenator failure, total number of circuit exchanges due to nonoxygenator failure, use of therapeutic anticoagulation during ECMO, and the mean activated partial thromboplastin time (aPTT) while on ECMO. For patients who were not fully anticoagulated, the reason for anticoagulation avoidance was documented. Propofol utilization was assessed by the mean of total propofol daily dose, total propofol ECMO dose, and total propofol dose used 48 hours before oxygenator failure in addition. In the daily mean activated partial thromboplastin time (aPTT) while on propofol, and the mean aPTT 48 hours before oxygenator failure were charted and used for analysis. The mean aPTT 48 hours before oxygenator failure for patients who did not receive propofol was likewise charted and used for analysis.

Additional factors that could have affected circuit integrity were also documented and analyzed. These included transfusions of platelets, fresh frozen plasma, cryoprecipitate, concentrated clotting factors, and other homeostatic agents. The use of parenteral nutrition (PN) was also recorded, noting administration or avoidance of lipid emulsion.

For all patients, ECMO therapy was executed using the Cardiohelp system with Quadrox oxygenator and polymethylpentene gas exchange membranes.

The study protocol was reviewed and approved by the Hamad General Hospital Institutional Review Board (MRC number-01-17-037).

### Definitions

Oxygenator membrane failure is simply defined as impairment in the oxygen or carbon dioxide exchange capabilities. Nonetheless, clinically, different centers use different criteria to define membrane failure. In our center, the final decision for circuit exchange is usually at the discretion of the treating ECMO-intensivist. However, predefined criteria are set and carried among all. A circuit exchange because of “oxygenator membrane failure” is usually indicated for the following scenarios:

1. Significant changes in the mechanical properties of the membrane, namely, increased impedance to flow, manifested by increased transmembrane pressure (\(\Delta dP\)), either gradually or suddenly (doubling of \(\Delta dP\), or any \(\Delta dP>50\) mm Hg).
2. Diminished oxygenation functionality of the membrane, exhibited as very low post-Oxygenator PaO\(_2\) and decrease in total O\(_2\) transfer through the membrane.
3. Diminished CO\(_2\) clearance as functionality of the membrane, characterized by persistently high PaCO\(_2\) despite escalation of the sweep gas flow and confirmed by decreased CO\(_2\) transfer through the membrane.

Circuit exchanges are also considered in circumstances not related to “oxygenator membrane failure.” These include:

1. Progressive unexplained DIC (Disseminated Intravascular Coagulopathy) even if gas exchange is not hugely impaired
2. Unexplained hemolysis
3. Acute pump head thrombosis (PHT), clinically defined by the sudden sound change of the pump (grinding sound) and mechanical-induced hemolysis +/- decrease of platelets
4. Suspected infection of the ECMO circuit (especially in cases of candidemia)
5. Other special cases (e.g., electively for travel reasons, port breakdown, or others).

Since the aim of this study was to investigate the association of propofol use and oxygenator failure, physicians’ notes and documented exchanges because of “oxygenator membrane failure” as defined by the previously mentioned criteria were considered for analysis and association. When circuit exchange was charted as elective, or was because of other reasons, it was reported in the overall number of circuit exchanges but not included in the analysis of “oxygenator failure and exchange.”

### Outcomes

The primary outcome of this analysis was to evaluate whether propofol use was associated with an increased risk of oxygenator failure. Cohorts who received propofol were compared with those who did not, and outcomes were assessed by means of duration of oxygenator functionality (in days) before an exchange was required, and number of oxygenator exchanges during propofol use and/or ECMO support days. The total duration of ECMO support (in days) was used as surrogate for oxygenator functionality in cases of no exchanges during ECMO.

Since the effects of not being fully anticoagulated was set as a priori subgroup analysis, patients who received propofol...
were further investigated for any increased risks of oxygenator failure as a function of anticoagulation avoidance.

For secondary outcomes, univariate and multivariate regressions of different factors that could theoretically affect oxygenator integrity were evaluated.

For all patients, assessment of clinical outcomes included duration of ECMO support and ICU discharge status.

Statistical Analysis

Statistical analyses were conducted using SPSS 26.0 software (SPSS Inc. Chicago, IL). Continuous variables are presented as mean ± SD for normally distributed data or as median/IQR for nonnormal distribution. Frequency (percentage) is used for categorical variables. An a priori subgroup analysis was conducted on the patients who did not receive therapeutic anticoagulation during ECMO run. Outcomes between groups (received propofol vs. did not receive propofol, or oxygenator failure vs. no oxygenator failure) were evaluated using \( \chi^2 \) test, Student's t test, and Mann-Whitney U test as indicated. Univariate and multivariate logistic regression models were considered if statistically significant at the \( p \)-value of <0.1 in the univariate analysis or if deemed by the research team as clinically important. Kaplan–Meier estimate was used for oxygenator life span comparisons. For all data, using a two-tailed comparison, a \( p \)-value of 0.80 and a \( p \)-value of <0.05 were deemed to have statistical significance.

RESULTS

Baseline Characteristics

A total of 82 patients required ECMO support within the included study period. Eighteen patients were excluded either because of receiving ECMO for less than 48 hours, or due to requiring modalities other than respiratory ECMO for support. One patient received respiratory ECMO support for underlying pulmonary tuberculosis, but as the ECMO support was prolonged (>6 months), the patient was excluded to prevent skewness of the results. Out of the 63 patients included in the analysis, 29 patients (46%) received propofol during ECMO support as part of their sedation regimen. The most common cause for requiring ECMO support was pneumonia (almost half of the included population). Baseline demographics and oxygenator clinical data did not differ significantly across the population groups (Table 1). The only exception was the duration of ECMO support, where patients tended to stay longer on ECMO support if they received propofol (\( p = 0.014 \)).

Circuit Exchange and Oxygenator Membrane Failure

Circuit exchange ensued at a relatively low rate across the whole population (a total of 15 exchanges for 11 patients in the studied sample). Of the 15 exchanged circuits, seven were not considered in the outcomes analysis as they were nonoxygenator failure-related (comprising two elective exchanges, one candidemia, one broken connection of dialysis port, and four for other reasons). Detailed demographics of all patients are presented in online supplementary material http://links.lww.com/ASAIO/A509. Thus, eight exchanges were considered in the final analysis of different clinical outcomes pertaining to oxygenator failure. Although failing to reach statistical significance, those who received propofol tended to have longer oxygenator running time as compared with controls (mean: propofol 23.3 days vs. control 17.6 days, \( p = 0.43 \)). Figure 1 shows freedom from oxygenator exchange across both groups.

Primary Outcomes

The use of propofol was not found to be associated with an increased incidence of circuit failure when compared with cohorts who did not receive propofol. Out of 29 patients in the propofol arm, 20.7% had oxygenator failure, as compared with 5.9% in patients who did not receive propofol (\( p = 0.129 \)). The median dose of propofol received during the whole ECMO run was 2427 mg (min, max, IQR: 150 mg, 72.426 mg, 6,015 mg).

Only two cases (33.3%) received propofol within 48 hours of oxygenator failure, with a mean dose of 940.46 mg. Surprisingly, receiving propofol 48 hours before circuit exchange was associated with decreased odds for circuit failure (OR 0.148, 95% CI: 0.06–0.366, P-value 0.037) when compared with those who had not received propofol within the studied time frame. Yet, it was noticed that patients who received propofol as part of their sedation regimen and experienced oxygenator failure tended to have received propofol for longer periods as compared with respective controls (\( p = 0.041 \), Table 2).

When analyzed for the effects of receiving anticoagulation and the correlated risk of circuit failure, the use of propofol was not found to be associated with an increased risk of circuit failure, even in the absence of anticoagulation during ECMO support (\( p = 0.631 \), Table 2). The different reasons for not receiving any form of intravenous anticoagulation (either full or premembrane) are presented in Figure 2. When analyzed across the whole population, oxygenator failure occurred at an equal rate of 12.5% when systemic anticoagulation was avoided, regardless of whether propofol was used or avoided (\( p = 0.464 \)).

Secondary Outcomes

Secondary outcomes were examined in the form of univariate (using \( \chi^2 \) test, online supplementary material http://links.lww.com/ASAIO/A509) and multivariate regression analyses to explore different predictors of oxygenator failure. The only predictor that seemed to statistically predict the risk of oxygenator failure in the univariate analysis was development of heparin-induced thrombocytopenia during ECMO course.

Multivariate regression analyses were computed for different predictors that were considered either statistically significant (using a cut-off of <0.05 or <0.2, as with Hosmer and Lemeshow testing), or clinically relevant. However, none of the tested regression resulted in a significant correlation.

DISCUSSION

Due to the increased rates of ECMO use worldwide, it has become prudent to evaluate different modalities commonly used in non-ECMO critically ill patients and validate their effectiveness among the ECMO population. Sedation plays a crucial part in the overall management of an ECMO patient, with
requirements ranging from minimal sedation (often referred to as “awake” patients) to deep sedations (or “medically induced coma”). Although appropriate sedation management is a cornerstone in managing ECMO patients, the literature describing it is scarce. Part of the challenge of sedation management during ECMO lies in the fact that higher dosing and requirements are often encountered in this population. Drug sequestration, adsorption, and loss in ECMO circuit have been well documented for different sedative agents commonly used in critically ill patients, including midazolam and propofol. This is usually coupled with the fact that, at least initially, many intensivists target deeper levels of sedation aiming to rest the lungs in cases of respiratory ECMO support or to stabilize the patient in cases of cardiac support. Consequently, higher dosing requirements are often encountered as compared with non-ECMO critically ill patients. The fast onset and offset actions, short-terminal half-life, minimal active metabolites, and lack of increased delirium risks, made propofol one of the first-line sedating agents employed across different cohorts of critically ill patients (i.e., medical, surgical, or neurologic). However, being a highly lipophilic derivative of phenol, the drug is often prepared as a lipid emulsion mixed with soybean oil, egg lecithin, and glycerol. This in turns results in a total of 100 milligrams of fats per each milliliter of administration (10% concentration). Previous literature had discouraged the use of fat emulsions during ECMO (including lipid emulsions used as part of parenteral nutrition or emulsions used in cases of treatments of different toxicological emergencies). This partly came from the observation of “layering” and “deposition” of fats within the ECMO circuit and subsequent clot formations despite maintaining adequate anticoagulation. Consequently, many intensivists avoided propofol as part of sedation regimens during ECMO.

Recently, interest in investigating the effects of propofol administration while on ECMO was regained, especially after the results of an in-vitro analysis confirming theoretical safety. In 2017, the first retrospective analysis of real ECMO patient data

### Table 1. Patient Demographics and Oxygenator Clinical Data

|                                | All patients (n = 63) | Received propofol (n = 29) | No propofol (n = 34) | p     |
|--------------------------------|-----------------------|---------------------------|---------------------|-------|
| Age, years (median, IQR)       | 31 (20)               | 37 (22.8)                 | 26 (18.5)           | 0.804 |
| Weight, kg (median, IQR)       | 70 (23)               | 65 (32.5)                 | 70 (32)             | 0.320 |
| Duration of ECMO support, days (median, IQR) | 12 (16)               | 48.5 (65)                 | 18 (11.5)           | 0.014*|
| Admission APACHE Score (mean, SD) | 25.79 (8.62)         | 24.83 (9.39)              | 29.6 (14.96)        | 0.185 |
| Gender (n, %)                  |                       |                           |                     | 0.681 |
| Male                           | 44 (68.8)             | 21 (72.4)                 | 23 (67.2)           |       |
| Female                         | 19 (30.2)             | 8 (27.6)                  | 11 (32.4)           |       |
| ICU discharge status (n, %)    |                       |                           |                     | 0.458 |
| Alive                          | 40 (63.5)             | 17 (58.6)                 | 23 (67.6)           |       |
| Dead                           | 23 (36.5)             | 12 (41.4)                 | 11 (32.4)           |       |
| HIT positive (n, %)            | 3 (4.8)               | 3 (10.3)                  | 0 (0)               | 0.055 |
| Indication for ECMO support (n, %) |     |                           |                     | 0.822 |
| Pneumonia                      | 33 (52.3)             | 15 (51.7)                 | 18 (52.9)           |       |
| CAP                            | 13 (20.6)             | 5 (17.2)                  | 8 (23.5)            |       |
| Viral pneumonia                | 11 (17.5)             | 6 (20.7)                  | 5 (14.7)            |       |
| Viral and superadded bacterial infection | 3 (4.8)             | 1 (3.4)                   | 2 (5.9)             |       |
| TB                             | 3 (4.8)               | 1 (3.4)                   | 2 (5.9)             |       |
| Aspiration                     | 3 (4.8)               | 2 (6.9)                   | 1 (2.9)             |       |
| Septic shock with nonidentifiable source | 12 (19)             | 7 (24.1)                  | 5 (14.7)            |       |
| Noninfectious cause            | 5 (7.9)               | 1 (3.4)                   | 4 (11.8)            |       |
| Polyttrauma                    | 13 (20.6)             | 6 (20.7)                  | 7 (20.6)            |       |
| Circuit exchange during whole ECMO run† |     |                           |                     | 0.533 |
| Yes                            | 11 (17.5)             | 6 (20.7)                  | 5 (14.7)            |       |
| No                             | 52 (82.5)             | 23 (79.3)                 | 29 (85.3)           |       |
| Oxygenator failure during ECMO |                       |                           |                     | 0.129 |
| Yes                            | 8 (12.7)              | 6 (20.7)                  | 2 (5.9)             |       |
| No                             | 55 (87.3)             | 23 (79.3)                 | 32 (94.1)           |       |
| Anticoagulation during whole ECMO run |     |                           |                     | 0.097 |
| Yes‡                          | 41 (65.1)             | 22 (75.9)                 | 19 (55.9)           |       |
| No                            | 22 (34.9)             | 7 (24.1)                  | 15 (44.1)           |       |
| Full anticoagulation 48 hours before circuit failure§ | | | | 0.632 |
| Full anticoagulation           | 1 (9.1)               | 1 (16.7)                  | 0 (0)               |       |
| Premembrane only               | 2 (18.2)              | 1 (16.7)                  | 1 (20.0)            |       |
| No anticoagulation             | 8 (72.7)              | 4 (66.6)                  | 4 (80)              |       |
| Circuit running time until first exchange, days (mean, SD) | 17.64 (16.3) | 23.33 (20.34)             | 10.8 (6.3)          | 0.429 |

*Significant difference, p < 0.05.
‡Yes = receiving any form of intravenous anticoagulation (either full anticoagulation or premembrane only).
§N = 11 patients.
†Reported as total number of patients who had any circuit exchange during ECMO. Some patients had multiple exchanges during ECMO run. Detailed demographics are presented in online supplementary material, Table 1.

APACHE, acute physiologic assessment and chronic health evaluation; CAP, community acquired pneumonia; ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; TB, tuberculosis.
was conducted by Hohfelder et al.\textsuperscript{17} and confirmed the possible safety of propofol without an increased risk of oxygenator failure. Later, in 2019, Lamm et al.\textsuperscript{18} reconfirmed the findings. Our results were in line with both trials. However, in the Hohfelder study, propofol use was mainly chosen for patients utilizing ECMO as a bridge to transplant, whereas in the Lamm group, it was more common in cardiac ECMO support cases. Both studies differ from ours. We chose patients who required ECMO for pure respiratory support, and excluded patients with cardiac ECMO support. Although in principle, such criteria may arguably appear similar to that of ECMO as a bridge to transplant, patients awaiting transplants are often awake and require minimal sedation, as opposed to acute hypoxemic patients requiring deep sedation levels and thus necessitating higher dosing.\textsuperscript{26,27} Cardiac cases were excluded from our analysis, since full anticoagulation is a prerequisite for VA-ECMO in our center and our \textit{a priori} sub-group analysis was aimed to compare effects of anticoagulation avoidance. Nonetheless, irrespective of the underlying setting, all three analyses (Hohfelder, Lamm, and current analysis) reported longer oxygenator running times associated with propofol utilization as compared with other controls. It worth noting that our analysis revealed higher risks of oxygenator failure associated with longer duration of propofol prescribing, a result that was similarly concluded by Hohfelder \textit{et al.}

Recently, running ECMO without therapeutic anticoagulation has been an area of interest in different researches.

\textbf{Table 2. Propofol Data}

| Outcome                                      | All Propofol Patients (n = 29) | Oxygenator Failure (n = 6) | No Oxygenator Failure (n = 23) | p     |
|----------------------------------------------|--------------------------------|----------------------------|-------------------------------|-------|
| Total duration of ECMO support (median, IQR)| 18 (20.5)                      | 48.5 (65)                  | 13 (15.3)                     | 0.011*|
| Total number of days received propofol (median, IQR) | 2 (5)                         | 11.5 (25.3)                | 2 (5)                         | 0.041*|
| Total dose of propofol received while on ECMO, mg (median, IQR) | 2427 (6015)                  | 18909.90 (51096)          | 1997.55 (3465)                | 0.059 |
| Propofol dose 48 hours before exchange, mg (median, IQR) | NA                           | 0 (2504.1)                 | NA                            | NA    |
| Number of days until first oxygenator exchange (mean, SD) | NA                           | 23.3 ± 20.34               | 15.6 ± 8.89†                 | 0.655 |
| Mean aPTT while on propofol                  | 39.5 ± 14.03                  | 40.2 ± 8.52                | 38.8 ± 15.47                 | 0.694 |
| Anticoagulation during ECMO (n, %)           |                                |                            |                               |       |
| Yes‡                                         | 22 (75.9)                     | 5 (83.3)                   | 17 (73.9)                     | 0.631 |
| No                                           | 7 (24.1)                      | 1 (16.7)                   | 6 (26.1)                      |       |
| HIT positive                                 |                                |                            |                               | 0.005*|
| Yes                                          | 3 (10.3)                      | 3 (50)                     | 0 (0)                         |       |
| No                                           | 26 (89.7)                     | 3 (50)                     | 23 (100)                      |       |

*Significant difference, P < 0.05.
†For patients who did not have circuit failure, oxygenator running time was considered equivalent to total duration of ECMO support.
‡Yes = Receiving any form of intravenous anticoagulation (either full or premembrane) at any time during ECMO support.
aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; IQR, interquartile range.
Hermann et al. 28 retrospectively reviewed the safety of respiratory ECMO running without anticoagulation for patients with thrombocytopenia and concluded the feasibility of running ECMO for longer periods without anticoagulants. Similarly, Krueger et al. 29 reported the feasibility without increased complications in the utilization of venous thrombosis prophylactic dosing. In our study, we investigated the effects of anticoagulation omission and risk of oxygenator failure among patients who received propofol to test the hypothesis of propofol safety in the absence of anticoagulation to prevent thrombus formation. Compared with controls who received other measures of sedation, propofol use without any form of anticoagulants (full or prophylactic) was not associated with increased odds of oxygenator failure. It also highlighted the feasibility of running respiratory ECMO without increased thrombosis risks in the absence of anticoagulation, confirming the results of other studies.28–30

We tried to investigate the effects of other cofactors that could have influenced the integrity of the ECMO circuit. The use of parenteral nutrition with lipid emulsion was investigated as a cofactor for increased oxygenator failure, based on the previous evidence associated with agglutination and layering. We found no significant association between the use of lipid emulsion with parenteral nutrition and oxygenator failure. Although the sample size was small (three patients of the population received parenteral nutrition containing lipid emulsion), our results nonetheless paralleled Lamm et al.’s, where they found no associated risks with lipid emulsion-containing TPN across a larger sample size (n = 33 patients).

The only risk factor for oxygenator failure was the development of heparin-induced thrombocytopenia (HIT) during ECMO. In 2016, Ratzlaff et al. 31 reported a similar case of oxygenator failure from HIT. Similarly, a recent review conducted by Choi et al. 32 reported 31% of circuit oxygenator thromboembolism occurring in HIT positive patients receiving VV-ECMO support, with more than half of the cases requiring oxygenator or circuit exchange. That HIT may result in a state of increased platelet adhesion and resultant thrombosis, although theoretically appealing, detailed investigation of this direct association might be warranted across a larger sample, as available evidence is limited to case reports or case series.

**LIMITATIONS**

Several limitations must be considered while interpreting the results of our analysis. First, because of its retrospective nature, and because our data collection included periods before the complete transition to electronic health records, some data were missing and could not be collected and analyzed. This included total propofol dose in one patient, or other pertaining labs that could be used for oxygenator integrity correlation (e.g., D-dimer, fibrinogen, triglycerides). Second, the wide variety of anticoagulation regimens utilized during a single ECMO run in some cases could have affected the interpretation of safety. Frequently, many patients bounced between full anticoagulation, premembrane fixed small dosing, and complete hold of anticoagulation during their runs. Because of this complexity, we combined patients who received any form of intravenous anticoagulation (premembrane and/or full anticoagulation) and compared them with those who never received any. Thus, the safety of each method (premembrane or full anticoagulation) compared with no anticoagulation or just prophylactic subcutaneous dosing may be worth further investigation. Finally, the use of propofol as a sedating method as well as a target dose (capped dosing in some cases) was completely left to the treating intensivist, and thus prescribing practices were never controlled. Although some patients received propofol, the dose was capped at smaller targets with the utilization of additional sedating agents in some patients, whereas others received dosing as needed based on a targeted sedation level. Thus, the effects of dosing received by patients and associated membrane failure may have been imbalanced.
CONCLUSION

Understanding of the optimal methods for sedating ECMO patients continues to evolve. The results of the current study further support the previously reported safety of propofol utilization during respiratory ECMO runs. Propofol use seemed safe regardless of whether patients were fully anticoagulated or not receiving any form of anticoagulants to prevent oxygenator failure. However, other cofactors that could affect oxygenator integrity (such as HIT) or the safety of propofol during cardiac ECMO support without anticoagulation may warrant further investigation.

REFERENCES

1. Marasco SF, Lukas G, McDonald M, McMillan J, Ihle B: Review of ECMO (extra corporeal membrane oxygenation) support in critically ill adult patients. *Heart Lung Circ* 17(Suppl 4): S41–S47, 2008.
2. Centers for Disease Control and Prevention (CDC): Outbreak of swine-origin influenza A (H1N1) virus infection—Mexico, March-April 2009. *MMWR Morb Mortal Wkly Rep* 58: 467–470, 2009.
3. DeLaney E, Smith MJ, Harvey BT, et al: Extracorporeal life support for pandemic influenza: the role of extracorporeal membrane oxygenation in pandemic management. *J Extr Corp Technol* 42: 268–280, 2010.
4. ELSO Registry Report International Summary: The Extracorporeal Life Support Organization (ELSO). Available at: https://www.elso.org/Registry/Statistics.aspx. Accessed November 8, 2019.
5. Zwischenberger J, Steinhorn R, Bartlett R (eds): ECMO: Extracorporeal Cardiopulmonary Support in Critical Care, 2nd ed. Ann Arbor, MI: Extracorporeal Life Support Organization, 2000.
6. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH: Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. *Intensive Care Med* 33: 1018–1024, 2007.
7. Ha MA, Sieg AC: Evaluation of altered drug pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation. *Pharmacotherapy* 37: 221–235, 2017.
8. Shekar K, Roberts JA, Mcdonald CL, et al: Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. *Crit Care* 19: 164, 2015.
9. Bhatt-Meht V, Annich G: Sedative clearance during extracorporeal membrane oxygenation. *Perturbation* 20: 309–315, 2005.
10. Muller H, Lawson G, von Anrep C, et al: In vitro evaluation of sedative drug losses during extracorporeal membrane oxygenation. *Perturbation* 15: 21–26, 2000.
11. Devlin JW, Skrobik Y, Gelinas C, et al: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 46: e825–e873, 2018.
12. Kam PC, Cardone D: Propofol infusion syndrome. *Anaesthesia* 62: 690–701, 2007.
13. Buck ML, Ksenich RA, Wooldridge P: Effect of infusing fat emulsion into extracorporeal membrane oxygenation circuits. *Pharmacotherapy* 17: 1292–1295, 1997.
14. Buck ML, Wooldridge P, Ksenich RA: Comparison of methods for intravenous infusion of fat emulsion during extracorporeal membrane oxygenation. *Pharmacotherapy* 25: 1536–1540, 2005.
15. Buscher H, Vaidyanathan S, Al-Soufi S, et al: Sedation practice in veno-venous extracorporeal membrane oxygenation: an international survey. *ASAIO J* 59: 636–641, 2013.
16. Myers GJ, Voorhees C, Eke B, Johnstone R: The effect of Diprivan (propofol) on phosphorylcholine surfaces during cardiopulmonary bypass—an in vitro investigation. *Perfusion* 24: 349–355, 2009.
17. Hohlfelder B, Szumita PM, Lagambina S, Weinhouse G, Degrado JR: Safety of propofol for oxygenator exchange in extracorporeal membrane oxygenation. *ASAIO J* 63: 179–184, 2017.
18. Lamm W, Nagler B, Hermann A, et al: Propofol-based sedation does not negatively influence oxygenator running time compared to midazolam in patients with extracorporeal membrane oxygenation. *Int J Artif Organs* 42: 233–240, 2019.
19. ELSO anticoagulation guideline. The Extracorporeal Life Support Organization (ELSO). Available at: https://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents.pdf. Accessed November 8, 2019.
20. deBacker J, Tamberg E, Munshi L, Burry L, Fan E, Mehta S: Sedation practice in extracorporeal membrane oxygenation-treated patients with acute respiratory distress syndrome: a retrospective study. *ASAIO J* 64: 544–551, 2018.
21. Shekar K, Roberts JA, Mullany DV, et al: Increased sedation requirements in patients receiving extracorporeal membrane oxygenation for respiratory and cardiorespiratory failure. *Anaesth Intensive Care* 40: 648–653, 2012.
22. Nigoghossian CD, Dzierba AL, Etheridge J, et al: Effect of extracorporeal membrane oxygenation use on sedative requirements in patients with severe acute respiratory distress syndrome. *Pharmacotherapy* 36: 607–616, 2016.
23. Cheng V, Abdul-Aziz MH, Roberts JA, Shekar K: Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *J Thorac Dis* 10(Suppl 5): S629–S641, 2018.
24. Bart JR: Propofol: A new drug for sedation in the intensive care unit. *Int Anaesthesiol Clin* 33: 131–154, 1995.
25. Baker MT, Naguib M: Propofol: the challenges of formulation. *Anaesthesiology* 103: 860–876, 2005.
26. Fuehner T, Kuehn C, Hadem J, et al: Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med* 185: 763–768, 2012.
27. Mohite PN, Sabashnikov A, Reed A, et al: Extracorporeal life support in “awake” patients as a bridge to lung transplant. *Thorac Cardiovasc Surg* 63: 699–705, 2015.
28. Hermann A, Schellongowski P, Bojic A, Robak O, Buctele N, Staudinger T: ECMO without anticoagulation in patients with disease-related severe thrombocytopenia: feasible but futile? *Artif Organs* 43: 1077–1084, 2019.
29. Krueger K, Schmutz A, Zieger B, Kalbhenn J: Venovenous extracorporeal membrane oxygenation with prophylactic subcutaneous anticoagulation only: an observational study in more than 60 patients. *Artif Organs* 41: 186–192, 2017.
30. Wen PH, Chan WH, Chen YC, Chen YL, Chan CP, Lin PY: Non-heparinized ECMO serves a rescue method in a multi-trauma patient combining pulmonary contusion and nonoperative internal bleeding: a case report and literature review. *World J Emerg Surg* 10: 15, 2015.
31. Ratzlaff RA, Ripoll JG, Kassab LL, Diaz-Gomez JI: Acute oxygenator failure: a new presentation of heparin-induced thrombocytopenia in a patient undergoing venovenous extracorporeal membrane oxygenation support. *BMJ Case Rep* 16: bcr2016218179, 2016.
32. Choi JH, Luc JGY, Weber MP, et al: Heparin-induced thrombocyto-penia during extracorporeal life support: incidence, management and outcomes. *Ann Cardiothorac Surg* 8: 19–31, 2019.