EDITORIAL

Prolonged VV ECMO: Navigating the Unchartered Sea

Vivek Kumar

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"To unpathed waters, undreamed shores" – William Shakespeare

The use of Veno-venous extracorporeal membrane oxygenation (VV ECMO) support for advanced respiratory failure, refractory to conventional mechanical ventilation, has increased over time, noticeably so during the COVID-19 pandemic. ECMO is labor and resource intensive, costly, with unpredictable outcomes. The duration of VV ECMO support is primarily defined by the trajectory of lung recovery which is interjected by several confounding factors – age, underlying cardiopulmonary reserve, preexisting organ dysfunction, aetiology and severity of the respiratory failure, lung mechanics, duration of mechanical ventilation preceding initiation of VV ECMO, degree of systemic inflammation, the severity of other organ dysfunction, development of nosocomial infections, use of anti-coagulation, development of VV ECMO related complications, and finally the delivery at a high or a low volume center. It is but natural that with so many variables the duration and trajectory of VV ECMO support is all but predictable. There are various definitions in literature for prolonged VV ECMO - >14 days, >21 days, and >28 days.

There is no answer to the question: Does prolonged VV ECMO guarantee survival? In this issue of the journal, Goel et al., 2023 retrospectively analyzed 22 cases who received prolonged VV ECMO >14 days for acute respiratory distress syndrome (ARDS) of varying aetiology at a single Tertiary Care Center in India. The aetiology of ARDS was COVID-19 (68.2%), H1N1 (9%), and pneumonia of unclear aetiology (22.8%); 77.3% had severe ARDS while 22.7% had moderate ARDS as per the Berlin criteria. The mean age was 54 years, 50% had a comorbid illness, the mean duration of mechanical ventilation prior to VV ECMO was 5 days, the mean baseline P/F ratio was 82, the mean Murray score was 3.5, 18.2% were on vasoactive support, 22.7% underwent proning post initiation of ECMO, and 90% were tracheostomized. The mean duration of ECMO support was 27.18 ± 11.59 days. 63.6% of patients received ECMO for a duration of 14–28 days while 36% received it for duration of >28 days. About 31.8% were successfully weaned off ECMO and discharged from the hospital. Minor bleeding was seen in 22.7% of patients, 13.6% had an acute kidney injury with 66% of these requiring renal replacement therapy; 9.1% of patients had pneumothorax, transaminitis, new onset shock post-ECMO initiation, and catheter-related bloodstream infection; 4.5% patients had an oxygenator failure and limb ischemia. Age was the only significantly different variable between survivors (mean 44 ± 8.1 years) and non-survivors (58.5 ± 10.1 years); there was no difference in the duration of ECMO support (24.7 ± 6.9 days in survivors versus 28.3 ± 13.2 days in non-survivors), and in the profile of complications between these groups. They concluded that the duration of ECMO support cannot be used to decide the futility or continuation of therapy.[1]

Department of Critical Care Medicine, Mahatma Gandhi Mission Medical College and Hospital, Navi Mumbai, Maharashtra, India

Corresponding Author: Vivek Kumar, Department of Critical Care Medicine, Mahatma Gandhi Mission Medical College and Hospital, Navi Mumbai, Maharashtra, India, Phone: +91 9833731099, e-mail: drvivekmd@rediffmail.com

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Friedrichson et al., 2021, retrospectively reviewed the use of VV ECMO for ARDS in 10801 patients between 2007 and 2018 from a German database and reported an overall hospital mortality of 54.4%. The hospital mortality was the highest in patients with VV ECMO duration of less than 2 days (69.7%, SD = 3.4%), and lowest in those with a duration of 6–8 days (43%, SD = 5.2%). The authors concluded that "this shows that patients who benefit from VV ECMO therapy need approximately one week before they can be weaned from ECLS with successful outcomes." They added that for patients dying in less than 2 days on VV ECMO, one needs to speculate whether the initiation was delayed or there was a questionable indication.[2] They attributed their higher mortality as compared to the CESAR (37%) and EOLIA (38%) trials, due to the strict inclusion criteria and delivery in specialized centers in these trials.[3,4]

Muguruma et al., 2020 retrospectively reviewed the use of ECMO in 1227 cases of respiratory failure between 2010 and 2018 in the Japanese national database. They found that the in-hospital mortality rate was 62.5% in low- (<8 cases/year), 54.7% in medium- (8–16 cases/year), and 50.4% in high-volume institutions (≥17 cases/year).[5]

Deatrick et al., 2019 retrospectively studied the outcomes of VV ECMO in 182 cases between 2014 and 2018. When stratified by age they found that the in-hospital mortality incrementally increased in patients above the age of 45 years; in-hospital survival was 84.6% for ages <45 years; and 67% ≥45 years ($p = 0.009$). They concluded that age is an independent predictor of survival to discharge and that patients above the age of 65 when treated with VV ECMO support for respiratory failure have low rates of survival to discharge.[6]

Neumann et al., 2023 retrospectively analyzed the data of 221 patients on VV ECMO support between 2007 and 2019 from Zurich. The in-hospital mortality was 37.6% and it did not statistically vary significantly between those with and without ARDS. They reported that increasing age (odds ratio (OR), 1.05), newly detected liver failure (OR, 4.83), red blood cell transfusion (OR, 1.91), and platelet

concentrate transfusion (OR, 1.93) were predictors of mortality. Bleeding complications were not an independent predictor of mortality.[7]

Chiu LC et al., 2015 retrospectively analyzed 65 patients receiving VV ECMO for ARDS between 2006 and 2011 from Taiwan. The hospital survival rate was 47.7%. They identified that younger age, shorter duration of mechanical ventilation before ECMO; lower APACHE II score, SOFA score, and MOD score, were associated with survival.[8] Sepsis syndrome with multiple organ failure has been described as the most common cause of death amongst patients with ARDS with less than 20% of deaths being attributed to refractory hypoxemia.[9,10]

Bergman et al., 2021 carried out a retrospective analysis on 46 patients who received VV- or VA-ECMO for COVID-19-related ARDS between March and November 2020 in ELSO-certified centers in Minnesota. They found a significantly lower age, higher peak pressures, higher P/F ratio, and a lower SOFA score, the last three just prior to ECMO cannulation; associated with 60-day survival following ECMO decannulation. The number of antibiotic days and the number of units transfused after ECMO initiation were significantly lower in survivors; while leukocytosis post-ECMO day 1–3, elevated D-dimer post-ECMO day 21–27, thrombocytopenia post-ECMO day 14 onwards, elevated CRP and ferritin levels post day 21 of ECMO cannulation were observed in non-survivors. They did not find any statistically significant difference between the duration of ECMO support between survivors and non-survivors. They concluded that "mortality is not related to the length of illness alone but is likely impacted by complications such as the severity of secondary infections".[11]

Dreier et al., 2021, retrospectively analyzed 16 patients with COVID-19-related ARDS at a Tertiary Care Center in Germany in 2020. They identified a shorter duration between the onset of symptoms and ECMO support, a lower SOFA score, shorter duration of mechanical ventilation, in-range ABG pH, higher hemoglobin, and lower activated partial thromboplastin time (aPTT) in ICU survivors. Amongst the complications, acute liver failure was seen more frequently in non-survivors. Oxygenator replacement was required more frequently in survivors. Median time on ECMO was not significantly different between survivors and non-survivors. Survivors were further divided into short-term (<28 days) and prolonged (≥28 days) ECMO groups.[12] The prolonged ECMO group had higher lung compliance prior to ECMO initiation which could reflect two different pathological subsets as described by Gattinoni et al.[13,14]

Russ et al., 2022 compared the duration of VV ECMO and ICU survival in a subset of 23 patients with COVID-19 and non-COVID ARDS. The median duration of VV ECMO support was similar between the two subsets but the duration of ECMO support was significantly more in survivors of COVID-19 as compared to non-COVID-19 ARDS; a median difference of 27 days.[15]

Flinspach et al., 2023 divided their patients into four groups based on the duration of VV ECMO support - <14 days, 14–27 days, 28–50 days, and >50 days. There was no difference in the in-hospital mortality between these groups. They concluded that the duration of VV ECMO support cannot be used for clinical decision-making to decide upon survival.[16]

Fisser et al., 2021 recently analyzed the performance of several scores: The RESP score, the PRESERVE score, the ROCH score, and the PRESET and general scores APACHE II, SOFA, and SAPS II to guide decision-making for which patients to support with VV ECMO. The PRESET score had the best though sub-optimal AUC value (0.658). The authors concluded that the use of such scores to decide about ECMO implementation in potential candidates should be discouraged.[17]

This elaborate insight into the multiple factors associated with mortality at all stages of illness for patients undergoing VV ECMO, in itself means that no single study or prediction score can capture all the variables. It is difficult to quantify the use of resources with cost being an important concern in India as most patients are uninsured. The study by Goel et al., 2023 also has similar limitations, and lack of proning before ECMO may reflect a less protocolized approach.[1]

The clinical decision-making for initiating and the ethical dilemma for discontinuing VV ECMO is still unresolved. Prolonged VV ECMO support gives the lung a chance to heal; the timeline and completion of recovery are uncertain. The best solution is to have a multi-disciplinary team and family involved with individualized decisions and hard endpoints for discontinuation.

If the journey is so unpredictable and the destination is nowhere in sight then how can the duration of this journey be used to predict outcomes.

Orcid

Vivek Kumar https://orcid.org/0000-0002-6914-5422

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