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# Large Dual-Lumen Extracorporeal Membrane Oxygenation Cannulas Are Associated with More Intracranial Hemorrhage

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## Abstract

Large dual lumen veno-venous (VV) extracorporeal membrane oxygenation (ECMO) cannulas may increase venous pressure in the brain, contributing to intracranial hemorrhage (ICH). A retrospective cohort study was performed using the extracorporeal life support organization (ELSO) registry. Propensity score matching was used to control for confounding. The rate of ICH and rates of hemolysis, cannula complications, and mortality were compared between adult patients with a smaller dual lumen cannula (27 to 30F) and patients with a large (≥31F) dual lumen cannula. 744 patients were included in the propensity score matched cohort. Patients were well matched except for residual imbalance in body weight and sex. Patients with a large cannula had an ICH rate of 4.3% compared to 1.6% in patients with a smaller cannula (p=0.03). There were no differences in hemolysis, cannula complications, or mortality between groups. After controlling for body weight and sex in the matched cohort, ICH odds remained higher in patients with a large cannula; OR=2.74, (95% CI=1.06 to 7.09, p=0.03). Our study data suggest that large

dual lumen VV ECMO cannulas are associated with more ICH and thus smaller cannulas may be preferable when feasible.

**Introduction**

Dual lumen veno-venous (VV) extracorporeal membrane oxygenation (ECMO) cannulas are used for adult patients with respiratory failure in many ECMO centers and have several potential advantages over conventional two site cannulation including: easier ambulation for patients, reduced sedation requirements, and earlier extubation.[1] Dual lumen cannulas are also associated with serious complications related to their size and design including: bleeding, migration into the right ventricle, and even right ventricular rupture.[2-3]

Patients with dual lumen VV ECMO cannulas have a high rate of intracranial hemorrhage (ICH). In one cohort of 72 patients with a dual lumen VV ECMO cannula the rate of ICH was 7%.[4] There are a number of factors that likely contribute to this high ICH rate including thrombocytopenia during ECMO, anticoagulation, and possibly intracranial venous hypertension from obstruction of the internal jugular vein and superior vena cava by the ECMO cannula. Further, a large number of

patients develop cannula associated deep venous thrombosis during ECMO, which may contribute to intracranial venous hypertension.[5]

Both smaller and large dual lumen VV ECMO cannulas are currently in use. At the present time, it remains unclear which cannula size is optimal for the "average" adult VV ECMO patient. In fact, there is a trade-off when considering which cannula size to use because a large cannula allows for greater ECMO blood flow, which improves oxygenation, but is also potentially associated with more cannula complications and a higher rate of cannula site bleeding.[2,4] To our knowledge, there are no clinical studies comparing outcomes between dual lumen cannula sizes. We hypothesized that large dual lumen VV ECMO cannulas would be associated with a higher rate of ICH than smaller cannulas given their larger size.

## Methods

*Subjects*

The extracorporeal life support organization (ELSO) registry was queried to identify all adult patients that had VV ECMO between 2011 and 2016 and had either a smaller (27 to 30F) or large (≥31F) dual lumen VV ECMO cannula. ELSO was not responsible for our data analysis or interpretation. Informed consent was waived as the study was not human subjects research and a de-identified dataset was used for the analysis. Patients that had a body weight above 150 kg or below 50 kg were excluded from the analysis.

*Variables*

For all patients we collected the following variables, which were available in the ELSO database: age, sex, body weight, cannula size, pre-ECMO arrest, FiO2 prior to ECMO, peak inspiratory pressure prior to ECMO, positive end expiratory pressure prior to ECMO, pH prior to ECMO, PaCO2 prior to ECMO, PaO2 prior to ECMO, intubation hours prior to ECMO, ECMO blood flow at 4 hours and 24 hours after ECMO initiation, and total ECMO hours.

*Outcomes*

The study's primary outcome variable was ICH, as defined in the ELSO registry. Secondary outcomes were significant hemolysis, cannula complications, and in-hospital mortality. Significant hemolysis is defined in the ELSO registry as plasma free hemoglobin level above 50 mg/dL.

*Sample size calculation*

Assuming a 7% rate of ICH in the high-risk group, an alpha of 5%, and 80% power, a total of 317 patients were needed in each group to detect a 50% lower ICH rate in the low-risk group.

*Statistical analysis*

Statistical analysis was performed using SAS 9.3 (SAS Corp, Cary, NC, USA). A propensity score model was created using logistic regression with the dependent variable being receipt of a smaller cannula and all the previously mentioned patient

and ECMO variables entered into the model as independent variables. After propensity scores were calculated for each patient, global optimal matching was used to create a propensity score matched cohort. Standardized differences were calculated to assess the balance of covariates in the matched cohort.

Both unadjusted and adjusted odds ratios with 95% confidence intervals were calculated for the primary outcome variable and for secondary outcome variables. Adjusted odds ratios controlled for variables that could not be fully balanced with the propensity score matching process.

**Results**

The propensity score-matched cohort included 744 patients. Patient characteristics for both groups with standardized differences are shown in Table 1. All covariates were well balanced between the two groups except for sex and body weight, which had some residual imbalance.

Table 2 shows study outcomes by cannula size group. Patients with a large cannula had an approximately 3-fold higher rate of ICH (4.3% vs. 1.6%, p=0.03). There were no significant differences in the rates of hemolysis, cannula complications, or mortality between the two groups (all p>0.05).

Table 3 shows both unadjusted and adjusted (for body weight and sex) odds ratios for study outcomes. The adjusted odds ratio for ICH with a large cannula remained

significant; OR=2.83 (95% CI=1.08 to 7.42) after adjusting for body weight and sex, but no other adjusted odds ratio was significant.

**Discussion**

Neurologic complications occur in 7% of patients on VV ECMO with ICH representing the most common form of injury (43%), followed by brain death (24%), and ischemic stroke (20.0%).[6] ICH is reported to occur in as many as 20% of adult ECMO patients, depending on the center, and is associated with a variety of risk factors including: high pre-cannulation SOFA coagulation score, low platelet count, and spontaneous extracranial hemorrhage .[7] The mortality rate for patients with ICH during ECMO is 81% at 1 month and 85% at six months, reflecting its devastating nature.[7] To our knowledge, no prior studies have evaluated whether cannulation strategy affects the rate of ICH in adult patients on VV ECMO. Cannulation strategy has the potential to impact ICH rates because dual lumen VV ECMO cannulas, 27F or greater, are larger than two site return cannulas, which are usually 19-23F for adult patients.

Dual lumen VV ECMO cannulas can be used in most adult patients who require VV ECMO and are associated with relatively low device failure and thrombosis rates.[8-9] Dual lumen VV ECMO cannulas are also associated with a relatively high complication rate of up to 38%. The most frequently reported complication is cannula site bleeding (20%), followed by cannula site infection (10%), and ICH (7%).[4]

The pathophysiology of ICH during VV ECMO is not fully understood, but is likely multifactorial and is related to platelet dysfunction, systemic anticoagulation, abnormal production of procoagulant factors during shock, loss of large vWF multimers, and intracranial venous hypertension from deep venous thrombosis (DVT) or cannula related obstruction of the internal jugular veins.[10-12] Bleeding complications are common in adult ECMO patients occurring in up to 50% of patients.[13] Cannula associated DVT is also common occurring in up to 85% of ECMO patients.[5] There are no animal studies confirming that VV ECMO cannulas cause venous congestion in the brain, but it is reasonable to assume that they increase cerebral venous pressure, as this phenomenon has been reported in patients with much smaller central venous catheters (8F), particularly in cases of bilateral internal jugular vein cannualtion.[14] Based on these observations, we hypothesized that large dual lumen VV ECMO cannulas would increase the risk for ICH and in fact our study data confirmed this.

A 27F dual lumen cannula can achieve maximum blood flows of approximately 4.5L/min, whereas a 31F cannula can achieve blood flows up to 6L/min.[15] Because oxygenation is directly related to ECMO blood flow, a large cannula offers a theoretical advantage in patients with severely impaired oxygenation. However, our analysis did not suggest any benefit from using a large cannula. In fact, patients in our cohort had comparable severity of pre-ECMO lung injury and ECMO blood flow at 4 and 24 hours was equivalent. In addition, there was no difference in

hemolysis between the two groups. These data suggest that adequate ECMO blood flow can be achieved in an "average" patient using either cannula without having to utilize excessively high RPMs. A smaller cannula may be preferable though because there appears to be less ICH.

Our study has several critical limitations. First, it was observational and data were pooled in the ELSO registry from multiple participating centers with highly variable practices. Second, although patients with a large cannula had more ICH they had the same mortality as patients with a smaller cannula. Unfortunately, the ELSO database does not have data on quality of life or functional outcome so it is difficult to discern whether there was a difference in functional survival between the two groups. Third, although we used propensity score matching to balance covariates between the groups, we cannot rule out the possibility of residual confounding which could have biased our results. In fact, we did not include some previously described risk factors for ICH in our propensity score analysis because these data were not readily available in the ELSO registry (eg: daily platelet counts, degree of anticoagulation, type of anticoagulation, and international normalized ratio values). Finally, in our cohort, the rates of ICH were 1% and 4% in the two groups. This is quite different from ICH rates reported in other studies, were ICH was as high as 20%.[6] Our rate of ICH is similar to that of the CESAR trial, but we cannot rule out the possibility of ICH under-reporting in the ELSO registry.[16]

In summary, our data suggest that large dual lumen VV ECMO cannulas are associated with more ICH than smaller cannulas. There was no difference in mortality, hemolysis, cannula complications, or ECMO blood flow at 4 and 24 hours between groups. Given these data, a smaller cannula may be preferable for most adult VV ECMO patients.

**References**

1. Kuhl T, Michels G, Pfister R, Wendt S, Langebartels G, Wahlers T: Comparison of the Avalon Dual-lumen Cannula with conventional cannulation technique for venovenous extracorporeal membrane oxygenation. Thorac Cardiovasc Surg 63: 653-62, 2015.

2. Chimot L, Marque S, Gros A, et al: Avalon Bicaval dual-lumen cannula for venovenous extracorporeal membrane oxygenation: survey of cannula use in France. ASAIO J 59: 157-61, 2013.

3. Banayan JM, Barry A, Chaney M: Right ventricular rupture during insertion of an Avalon elite catheter. J Cardiothorac Vasc Anesth 30: e34-5, 2016.

4. Rubino A, Buylsteke A, Jenkins D, Fowles JA, Hockings L, Valchanov K: Direct complications of the Avalon bicaval dual-lumen cannula in respiratory extracorporeal membrane oxygenation (ECMO): single-center experience. Int J Artif Org 37: 727-800, 2014.

5. Menaker J, Tabatabai A, Rector R, et al: Incidence of cannula associated deep venous thrombosis after veno-venous extracorporeal membrane oxygenation. ASAIO J 63: 588-91, 2017.

6. Lorusso R, Gelsomino S, Parise O, et al: Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the extracorporeal life support organization database. Crit Care Med 45: 1389-97, 2017.

7. Fletcher-Sandersjoo A, Bartek J, Thelin EP, et al: Predictors of intracranial hemorrhage in adult patients on extracorporeal membrane oxygenation: an observational cohort study. J Intensiv Care 5: 27, 2017.

8. Javidfar J, Brodie D, Wang D, et al: Use of bicaval dual-lumen catheter for adult venovenous extracorporeal membrane oxygenation. Ann Thorac Surg 91: 1763-8, 2011.

9. Gothner M, Buchwald D, Strauch JT, Schildhauer TA, Swol J: The use of double lumen cannula for veno-venous ECMO in trauma patients with ARDS. Scand J Trauma Resusc Emerg Med 23: 30, 2015.

10. Abrams D, Baldwin MR, Champion M, et al: Thrombocytopenia and extracorporeal membrane oxygenation in adults with acute respiratory failure: a cohort study. Intensive Care Med 42: 844-52, 2016.

11. Cheung PY, Sawicki G, Salas E, Etches PC, Schulz R, Radomski MW: The mechanisms of platelet dysfunction during extracorporeal membrane oxygenation in critically ill neonates. Crit Care Med 28: 2584-90, 2000.

12. Tauber H, Ott H, Streif W, et al: Extracorporeal membrane oxygenation induces short-term loss of high molecular weight von willebrand factor multimers. Anesth Analg 120: 730-6, 2015.

13. Mazzeffi M, Greenwood J, Tanaka K, et al: Bleeding, transfusion, and mortality on extracorporeal life support: ECLS working group on thrombosis and hemostasis. Ann Thorac Surg 101: 682-9, 2016.

14. Stocchetti N, Longhi L: Bilateral cannulation of internal jugular veins may worsen intracranial hypertension. Anesthesiology 99: 1017-18, 2003.

15. https://www.getinge.com/int/product-catalog/avalon-elite-bi-caval-dual-lumen-catheter/ Accessed August 18th, 2018.

16. Peek GJ, Mugford M, Tiruvoipati R, et al: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374:1351-63, 2009.

Table 1. Patient characteristics in propensity score matched cohort

| Variable | 27-30F N=372 | ≥31F N=372 | SD |
|---|---|---|---|
| Age | 45 ± 16 | 46 ± 14 | 0.07 |
| Weight (kg) | 78 ± 19 | 82 ± 18 | 0.22 |
| Sex (% male) | 150 (40.3) | 193 (51.9) | 0.23 |
| Pre ECMO arrest | 24 (6.5) | 23 (6.2) | 0.01 |
| Fio2 | 1.0 [1.0, 1.0] | 1.0 [1.0, 1.0] | <0.01 |
| Peak inspiratory pressure | 35 [30, 40] | 35 [30, 40] | <0.01 |
| PEEP | 14 [10, 16] | 14 [10, 17] | 0.02 |
| pH prior to ECMO | 7.24 [7.14, 7.35] | 7.25 [7.15, 7.34] | 0.06 |
| PCO2 prior to ECMO | 56 [43, 72] | 54 [42, 73] | <0.01 |
| PO2 prior to ECMO | 58 [44, 71] | 56 [44, 71] | 0.08 |
| Intubation hours prior to ECMO | 48 [17, 133] | 48 [16, 140] | 0.03 |
| Pump flow 4 hours | 4.2 [3.7, 4.7] | 4.2 [3.6, 4.8] | 0.03 |
| Pump flow 24 hours | 4.2 [3.8, 4.75] | 4.3 [3.8, 4.9] | 0.08 |
| Total ECMO hours | 166 [87, 354] | 184 [93, 363] | 0.03 |

values are median [interquartile range] or number (% of patients)
ECMO=extracorporeal membrane oxygenation, PEEP=positive end expiratory pressure, SD=standardized difference

Table 2. Patient outcomes

| Variable | 27-30F | ≥31F | p value |
|---|---|---|---|
| | N=372 | N=372 | |
| Intracranial hemorrhage | 6 (1.6) | 16 (4.3) | 0.03 |
| Hemolysis | 17 (4.6) | 24 (6.5) | 0.26 |
| Cannula complication | 23 (6.2) | 21 (5.6) | 0.76 |
| In hospital mortality | 145 (39.0) | 145 (39.0) | 1.0 |

values are number (% of patients)

Table 3. Adjusted and unadjusted odds ratios for outcomes with large versus smaller cannulas

| | OR | 95% CI | p value |
|---|---|---|---|
| **ICH** | | | |
| Unadjusted | 2.74 | 1.06 to 7.09 | 0.03 |
| Adjusted for sex and weight | 2.83 | 1.08 to 7.42 | 0.03 |
| **Hemolysis** | | | |
| Unadjusted | 1.44 | 0.76 to 2.73 | 0.26 |
| Adjusted for sex and weight | 1.45 | 0.76 to 2.77 | 0.26 |
| **Cannula complication** | | | |
| Unadjusted | 0.91 | 0.49 to 1.67 | 0.76 |
| Adjusted for sex and weight | 0.99 | 0.53 to 1.84 | 0.97 |
| **Mortality** | | | |
| Unadjusted | 1.0 | 0.75 to 1.34 | 1.0 |
| Adjusted for sex and weight | 0.99 | 0.74 to 1.34 | 0.97 |

CI=confidence interval, ICH=intracranial hemorrhage, OR=odds ratio