Association between arterial carbon dioxide, brain biomarkers and central nervous system injury during veno-venous extracorporeal membrane oxygenation: A Prospective Cohort Study.

Sonny Thiara (thiarasonny@gmail.com)
The University of British Columbia

Sophie Stukas
The University of British Columbia

Ryan Hoiland
The University of British Columbia

Cheryl Wellington
The University of British Columbia

Mike Tymko
The University of British Columbia

George Isac
The University of British Columbia

Gordon Finlayson
The University of British Columbia

Hussein Kanji
The University of British Columbia

Kali Romano
The University of British Columbia

Veronica Hirsch-Reinshagen
The University of British Columbia

Mypinder Sekhon
The University of British Columbia

Donald Griesdale
The University of British Columbia

Research Article

Keywords: Veno-venous extracorporeal membrane oxygenation, brain biomarkers, central nervous system, intracranial hemorrhage, ischemic stroke
Abstract

Background

Central nervous system (CNS) injury following initiation of veno-venous extracorporeal membrane oxygenation (VV-ECMO) is common. An acute decrease in PaCO\textsubscript{2} following VV-ECMO initiation has been suggested as an etiological factor, but the challenges of diagnosing CNS injuries has made discerning a relationship between PaCO\textsubscript{2} and CNS injury difficult.

Methods

We conducted a prospective cohort study of adult patients undergoing VV-ECMO for acute respiratory failure. We collected blood biospecimens to measure brain biomarkers (neurofilament light [NF-L]; glial fibrillary acidic protein [GFAP]; and phosphorylated-tau 181 [p-tau 181]) in the first seven days following initiation of VV-ECMO. We assessed the relationship between both PaCO\textsubscript{2} over the first 24-hours and brain biomarkers with CNS injury using mixed methods linear regression.

Results

In our cohort twelve of 59 (20%) patients had overt CNS injury identified on head CT. The PaCO\textsubscript{2} decrease with VV-ECMO initiation was steeper in patients who developed a CNS injury (-0.32%, 95%CI: -0.25 to -0.39) compared to those without (-0.18%, 95%CI: -0.14 to -0.21, P-interaction < 0.001). The mean concentration of NF-L increased over time and was higher in those with a CNS injury (464 [739]) compared to those without (127 [257]) (P = 0.001). GFAP was higher in those with a CNS injury (4278 [11653] pg/ml) compared to those without (116 [108] pg/ml) (P < 0.001).

Conclusions

Although rapid decreases in PaCO\textsubscript{2} following initiation of VV-ECMO were slightly greater in patients that had CNS injuries vs. those without, data overlap and absence of relationships between PaCO\textsubscript{2} and brain biomarkers suggests other pathophysiologic variables are likely at play.

INTRODUCTION

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) enables \textit{ex-vivo} gas exchange (oxygenation and removal of carbon dioxide) in critically ill patients with acute respiratory failure\textsuperscript{1} and mitigates ventilator-induced lung injury\textsuperscript{1,2}. The use of VV-ECMO to manage patients with refractory acute respiratory distress syndrome (ARDS) has increased in recent years due to improvements in portability\textsuperscript{3}, simplicity of the extra-corporeal circuit\textsuperscript{4}, and with the emergence of the Coronavirus Disease 2019 (COVID-19) pandemic\textsuperscript{5,6}.  

Page 3/18
Although VV-ECMO can be lifesaving, its use is associated with significant complications\(^7\). Specifically, central nervous system (CNS) injury (e.g., intracerebral hemorrhage and/or ischemic infarction) following the initiation of VV-ECMO is associated with increased mortality and adverse long-term functional outcomes\(^8,9,10,11\). Historical cohort studies suggest that among adult patients with acute respiratory failure undergoing VV-ECMO, the incidence of CNS injury ranges from 7 to 50\%\(^9\). Importantly, in-hospital mortality in patients with CNS injury is greater than 75\%, compared to less than 40\% in those without CNS injury\(^8,9\).

One potential mechanism of CNS injury following VV-ECMO initiation is thought to be related to a precipitous decrease in arterial carbon dioxide (PaCO\(_2\)) and consequent cerebral vasoconstriction and hypoperfusion\(^12,13\). Previous studies have linked PaCO\(_2\) reductions following ECMO to heterogeneous composite definitions of CNS injuries\(^14,15\) encompassing seizures, ischemic stroke, intracranial hemorrhage, or brain death\(^9\). These studies have also modeled various ‘exposures’ of PaCO\(_2\), such as the immediate reduction on initiation of VV-ECMO\(^14\) and comparing pre-VV-ECMO value to the PaCO\(_2\) at 24 hours following initiation\(^15\). However, ascribing fixed thresholds of PaCO\(_2\) does not adequately reflect the trajectory of this continuous variable over time. In addition, the timing and characterization of CNS injury in patients undergoing VV-ECMO are also unclear. The diagnosis of CNS injury relies upon clinical examination or head computed tomography (CT)\(^16\), both of which are limited in patients undergoing VV-ECMO due to patient sedation and transport logistics respectively. Moreover, clinical examination may underestimate the true occurrence of CNS injury\(^17\). Thus, alternate methods to identify patients with a CNS injury in a timely matter are needed.

Blood-based brain injury biomarkers have been increasingly studied to characterize the timing, severity, and mechanism(s) of CNS injury in traumatic brain injury and Alzheimer’s disease\(^18,19,20,21\). Glial fibrillary acidic protein (GFAP) is a component of the astrocytic cytoskeleton, highly specific to the CNS, and reflects astroglial activation and/or injury\(^18\). Phosphorylated tau protein (p-tau 181) and neurofilament light (NF-L) reflect injury primarily in axons\(^19,20,21\), and myelinated white matter. Each of these biomarkers, have been used to assess the severity of ischemic brain injury\(^22\), and are instantaneously released during brain hypoxia\(^23\), thereby holding promise as acute diagnostic tools to assess of CNS injuries in critically ill patients.

Therefore, we conducted a prospective observation cohort study in patients undergoing VV-ECMO with three aims. First, we sought to characterize the relationship between acute reductions in PaCO\(_2\) following initiation of VV-ECMO and CNS injury detected with clinical examination. We hypothesized that more rapid reduction in PaCO\(_2\) around the time of initiation of VV-ECMO would be associated with CNS injury. Second, we sought to assess the association between biomarkers of neurologic injury and CNS injuries detected with clinical examination. We hypothesized that serum levels would be significantly greater in patients with CNS injuries compared to those without. Third, we aimed to examine the relationship between changes in PaCO\(_2\) following the initiation of VV-ECMO and biomarkers of brain injury. We
hypothesized that greater reductions in PaCO$_2$ following initiation of VV-ECMO would be associated with increased serum biomarker levels (Fig. 1).

**METHODS**

We conducted a prospective observational cohort study of 59 consecutive adult patients who received VV-ECMO at Vancouver General Hospital (VGH) Intensive Care Unit (ICU). UBC Clinical Research Ethics Board approval was obtained for the study (H21-00033 / H20-00971) and informed consent was obtained from the patient's legal authorized representative.

**Study setting, management, and population**

The ICU at VGH is a closed, 40 bed, mixed medical-surgical unit with a 1:1 nursing to patient ratio and intensivists with sub-specialty training in VV-ECMO. On-site perfusion specialists are in attendance to guide ongoing provision of VV-ECMO. Cannulation with percutaneous Seldinger technique is guided by ultrasound$^{25}$ with standardized right femoral vein access (23-27Fr) and right internal jugular vein (15–19 Fr) return lines. Cardiohelp (Gothenburg, Sweden) or Sorin (London, United Kingdom) devices are used. Unfractionated heparin (5000 Unit intravenous bolus) is administered prior to initiation of VV-ECMO and the sweep gas is set between 1 to 3 L/min to minimize precipitous reductions in PaCO$_2$. Heparin infusions are titrated using a standardized protocol for a partial thromboplastin time (PTT) target of 50–70 seconds while on VV-ECMO. Other management decisions are standardized including mean arterial pressure > 65 mmHg, arterial oxygen tension (60–100 mmHg), normothermia (36 to 37.5$^\circ$C). The primary sedatives used are intravenous propofol, hydromorphone, and ketamine. The primary vasopressor used is norepinephrine. Management is reflective of ELSO recommendations$^{25}$.

We included patients who were greater than 18 years of age undergoing VV-ECMO for acute respiratory failure. We excluded patients with either a pre-existing history of chronic CNS injury (or neurodegenerative disorder), or pre-existing known CNS injury (traumatic brain injury, stroke, intracranial hemorrhage, hypoxic ischemic brain injury following cardiac arrest).

**Data sources, measurement, and outcomes**

In addition to demographic data, we collected the following using a Research Electronic Data Capture (REDCap) (H14-00930) database$^{23}$ based on ELSO definitions: VV-ECMO related complications (e.g. CNS injury, bleeding, organ failure, infection, death), circuit complications (e.g. oxygenator failure, air embolism, pump thrombosis), and clinical physiological parameters (e.g. hourly mean arterial pressure, body temperature, sedative and vasopressor doses). Timing of arterial blood gas measurements were obtained prior to initiation of VV-ECMO, and at every 2–4 hours for the first 24 hours. Bio-specimens collected for the analysis of brain biomarkers were obtained at 4 time points via an in situ arterial line: immediately prior to VV-ECMO initiation, and at 1-hour, 24-hours and 7-days following the initiation of VV-ECMO. Samples were collected in serum separator tubes (Becton & Dickinson, Vacutainer, 367986), set
upright in the dark for 10 minutes then centrifuged at 600 g for 10 minutes, with the serum supernatant aliquoted into cryovials and immediately frozen in a -80-degree Celsius freezer. Plasma concentrations of NF-L and GFAP were quantified using the Neuro-4-plex-E advantage assay (cat no. 103670) and p-tau-181 V2 advantage assay (cat no. 103714) using the Quanterix Simoa HD-X platform following the manufacture's protocol.

**Neurologic outcomes**

CNS injury was defined as either a new intracranial hemorrhage or infarct on CT imaging of the brain. Neuroimaging is conducted as part of routine care within the first 7–14 days for most patients managed with VV-ECMO in our institution who require ongoing intravenous sedation thereby confounding the clinical examination. Patients without neurological deficits off sedation, and who did not have a CT scan, were considered to not have CNS injury.

**Statistical Analysis**

*Relationship between PaCO\(_2\) and neurologic outcome.*

We first visually assessed the relationship by plotting PaCO\(_2\) (connected line plot for each patient) over time stratified by injury status. Because of the non-linear relationship between PaCO\(_2\) and time, we performed a logarithmic transformation of PaCO\(_2\) prior to fitting our model. We then performed a mixed-effects linear regression of ln(PaCO\(_2\)) on injury (dichotomous variable), specifying ‘patient’ as a random-effect (STATA command *xtreg*). In order to assess for effect measure modification, we also included an interaction variable of time and injury.

To assess previously published relationships of changes in PaCO\(_2\) and CNS injury\(^{14,15}\), we dichotomized PaCO\(_2\) exposure in three separate ways. First, we compared those patients with an absolute change (\(\Delta\)) of PaCO\(_2\) of \(\geq 27\) mmHg compared to those with a \(\Delta\)PaCO\(_2\) < 27 mmHg on initiation of VV-ECMO (threshold identified by Luyt et al\(^{14}\)). Second, we calculated the pre-post percentage (PP%) as the difference between the PaCO\(_2\) obtained immediately prior to VV-ECMO, and 24-hours after initiation, divided by the pre-VV-ECMO PaCO\(_2\) at the 50% threshold (per Cavayas et al\(^{15}\)). Third, we calculated the Max-Min percentage (MM%) as the highest minus the lowest PaCO\(_2\) in the first 24 hours of VV-ECMO divided by the pre-VV-ECMO PaCO\(_2\) (a novel metric). We then assessed the relationship between all three PaCO\(_2\) variables with CNS injury using univariable logistic regression. Finally, as part of a post-hoc sensitivity analysis, we explored different thresholds for \(\Delta\)PaCO\(_2\) MM%.

**Relationship between brain biomarkers and CNS injury**

We first visually assessed NF-L, GFAP and p-tau 181 over time (connected line plot for each patient) and stratified by injury status. Because of the non-linear relationship between NF-L and GFAP with time, we performed a logarithmic transformation of the biomarker values prior to fitting a model. We then performed separate mixed-effects linear regression for each biomarker using CNS injury as a
dichotomous predictor variable and specifying “patient” as a random-effect (STATA command *xtreg*). To assess for effect measure modification, we also included an interaction variable of time (indicator variables) and injury.

**Post hoc exploratory analysis**

To explore the effects of \(\Delta PaCO_2\) on serum levels of neurological biomarkers, we performed separate mixed-methods linear regression for each biomarker using three \(PaCO_2\) exposures (reduction on initiation of VV-ECMO \(\geq 27\)mmHg, \(\Delta PaCO_2\) PP > 50% and \(\Delta PaCO_2\) MM \(\geq 50\%\)) as a dichotomous predictor variable and specifying “patient” as a random-effect in patients.

All analyses were two-sided, we considered a \(P\) value < 0.05 statistically significant and analyses were performed with Stata 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

**RESULTS**

We enrolled 59 patients between April 1st, 2020, and November 30th, 2021. The mean (SD) age was 50 (10) years and 11 (17%) were female. Fifty (85%) patients required VV-ECMO for respiratory failure secondary to COVID-19 (Table 1). Twelve patients (20%) developed a CNS injury post VV-ECMO initiation, of which 9 patients had an intracranial hemorrhage and 3 patients had an ischemic infarct. Median time to diagnosis was 9.5 [7-15.5] and 17.5 [3–47.5] days from the initiation of VV-ECMO for patients with an intracranial hemorrhage or ischemic stroke, respectively. Overall survival to ICU discharge 66% (39/59), which was 25% (3/12) in the CNS injury group and 77% (36/47) in those without CNS injury. \(PaCO_2\) pre VV-ECMO was 68 mmHg [54–76] in the CNS injury group and 70 mmHg [58–94] in those without CNS injury (OR 1.02, 95%CI: 0.99 to 1.04).

**Relationship between \(PaCO_2\) and neurologic outcome.**

\(PaCO_2\) values over first 24 hours were analyzed over time in patients with and without CNS injury (Fig. 2). After logarithmic transformation, \(PaCO_2\) decreased over time in all patients (-0.21% per 10 minutes, 95%CI: -0.17 to -0.24). There was effect measure modification of the \(PaCO_2\) over time by CNS injury (P-interaction < 0.001). Patients with CNS injury had a steeper reduction in \(PaCO_2\) by -0.32% (95%CI: -0.25 to -0.39) for each 10 minutes compared to a reduction of \(PaCO_2\) by -0.18% (95%CI: -0.14 to -0.21) in those without CNS injury. Post-hoc analysis of various \(PaCO_2\) thresholds is shown in the Electronic Supplementary Material (E-Table 1). Accordingly, \(\Delta PaCO_2\) MM%\(\geq 50\%\) in first 24 hours was associated with an increased odds of CNS injury (OR 8.8, 95%CI: 2.0 to 37.8). However, neither \(PaCO_2\) reduction on initiation of VV-ECMO \(\geq 27\)mmHg (OR 1.0, 95%CI: 0.9 to 1.0), nor \(\Delta PaCO_2\) PP% \(>50\%\) (OR 3.6, 95% CI 0.7 to 18.9) were associated with CNS injury.
Relationship between brain biomarkers and CNS injury

Baseline brain biomarker levels stratified by CNS-injury are presented in E-Table 2 and Fig. 3. The mean (SD) NF-L level over time was higher in the CNS injury group (464 [739] pg/ml) compared to those without (127 [257] pg/ml) (P < 0.001). NF-L levels were higher at each time-point (including pre VV-ECMO) in the CNS injury group and increased over time for both groups. There was no interaction of time by CNS injury for NF-L (P-interaction = 0.43). For GFAP, the mean levels over time were higher in the CNS injury group (4278 [11653] pg/ml) compared to those without (116 [108] pg/ml) (P < 0.001). GFAP did not increase over time and there was no interaction between time and CNS injury (P-interaction = 0.23). There was no difference in p-tau 181 over time in the CNS injury group compared to those without, (2.1 [1.6] vs. 1.5 [1.4] pg/ml, P = 0.14), and there was no interaction between injury and time (P-interaction = 0.63).

Post hoc exploratory analysis of changes in PaCO$_2$ and biomarkers of neurologic injury

E-Figure 1 is the mean NF-L, GFAP and tau over time in patients stratified by the three thresholds of ΔPaCO$_2$ (≥ 27 mmHg vs. <27 mmHg; PP ≥ 50% vs. < 50%; MM ≥ 50% vs. <50%). There were no differences in mean NF-L, GFAP or p-tau 181 at baseline and no significant interaction for time for NF-L, GFAP or tau.

DISCUSSION

We present a prospective observational study investigating the role of PaCO$_2$ reduction in VV-ECMO associated CNS injury pathophysiology and shed light on the relationships of brain biomarkers to CNS injury in VV-ECMO. Although we observed a greater statistical reduction in PaCO$_2$ in those with a CNS injury compared to those without, visual examination of this relationship does not support an overwhelming difference in the magnitude of this relationship between groups. Previously defined reductions of PaCO$_2$ on initiation of VV-ECMO and the comparison of values 24 hours apart, are likely not the sole explanation for the etiology of VV-ECMO associated CNS injury and a Max-Min percentage of PaCO$_2$ in first 24 hours of VV-ECMO may be better exposure variable to represent the PaCO$_2$ effects on CNS injury. In the biomarker analysis, we demonstrated that systemically circulating levels of NF-L and GFAP were greater in patients who developed a CNS injury. Furthermore, there was a progressive increase in NF-L during the first 7 days regardless injury status. Finally, we did not observe relationships between various thresholds of PaCO$_2$ reduction following initiation of VV-ECMO and systemically circulating brain biomarker levels.

Our study focused on evaluating the proposed pathophysiology relating the acute reduction of PaCO$_2$ to CNS injuries. Although we observed a slightly steeper reduction in PaCO$_2$ in patients with CNS injury compared to those without, given the significant overlap in data, similarity in the appearance of the curves and small number of outcomes (n = 12), it is questionable that PaCO$_2$ is the sole driver of the
pathophysiology for VV-ECMO associated CNS injury. Instead, our data points to a more complex picture in which alternative and perhaps unknown mechanisms, are at play. Luyt et al examined 135 consecutive patients on VV-ECMO and demonstrated that intracranial bleeding was associated with $\Delta PaCO_2$ decrease $\geq$ 27mmHg (OR 6.0, 95% CI: 1.2 to 30.0) following initiation of VV-ECMO$^{14}$. In a large historical analysis of 11,972 patients in the Extracorporeal Life Support Organization Registry, Cavayas et al showed that a $\Delta PaCO_2$ PP reduction > 50% was associated with neurological complications (OR 1.7, 95% CI 1.3 to 2.3)$^{15}$. In each case, the definition of CNS injuries has been heterogeneous with a composite outcome of cerebral hemorrhage, ischemia, seizures, and neurological brain death$^{15}$. Further, retrospective designs hinder the strength of these conclusions. Clinical assessment of CNS injury may also underestimate pathology determined CNS injury. Given our hypothesis that the trajectory of PaCO$_2$ changes upon VV-ECMO initiation may lead to CNS injury, we explored various thresholds of $\Delta PaCO_2$ MM% in first 24 hours and found that a MM $\% \geq 50$ (OR 8.8, 95%CI: 2.0 to 37.8) may represent a PaCO$_2$ exposure that requires further validation in its effects on CNS injury.

We also observed that two biomarkers of neurologic injury, NF-L and GFAP, were elevated in patients who developed a CNS-injury. Furthermore, NF-L was elevated prior to initiation of VV-ECMO in those patients who developed CNS-injury. This latter finding suggests that there could be an unrecognized neurologic injury prior to cannulation that is related subsequent determination of CNS injury post cannulation via clinical exam or neuroimaging. Unfortunately, current diagnostic modalities are limited in this patient population. For example, clinical examination is often confounded by sedative use, and CT imaging is challenging in patients who are physiologically unstable$^{16}$. Therefore, brain biomarkers represent an objective and quantitative diagnostic tool that might overcome these limitations and identify at risk patients who may develop CNS injury following VV-ECMO initiation. Given that brain biomarkers are associated with adverse outcome in neurologically injured patients after cardiac arrest and traumatic brain injury, there is promise for their use in patients requiring VV-ECMO$^{22,28}$. Further, Hoiland et al. demonstrated release of NF-L and GFAP in patients with brain tissue hypoxia, a physiologic perturbation which may occur following VV-ECMO initiation due to PaCO$_2$ related reductions in cerebral blood flow and consequent hypoperfusion$^{24,14}$. Notwithstanding the limitations of the small sample size in our study, these biomarkers of neurologic injury did not appear to be related to changes in PaCO$_2$.

It should be noted that although NF-L and GFAP levels were greater in VV-ECMO patients with overt CNS injuries, their systemically circulating levels in patients without injury were greatly increased compared to normative values in healthy controls$^{24,27}$. This finding raises the possibility that there may be subclinical CNS injury following initiation of VV-ECMO that is not detectable on CT. The pathophysiologic pattern of injury, natural history and clinical sequelae are unknown and represent key research areas for the future.

Our study should be viewed within the context of its strengths and also limitations. In terms of strengths, we conducted a prospective design with timed biomarker sampling in relation to the timing of VV-ECMO. Our study also used a highly sensitive analytical platform to assess brain biomarkers$^{29}$ which are closely related to clinical outcome assessment in neurologically injured patients, shown to have instantaneous
release in setting of brain hypoxia and are brain-specific in their tissue of origin. Limitations of this study include our relatively small sample size, single center study design and our selection of a composite outcome of intracerebral hemorrhage or ischemia to denote CNS injury. Importantly, these entities may represent different mechanisms of cerebral injury. Given the inability to do daily neurological examinations or CT imaging of patients on VV-ECMO, the timing of CNS injury remains unclear. Further, our number of CNS events is relatively small and future work to assess the diagnostic utility of brain biomarkers in this population should be multicenter to increase statistical power and strengthen external validity. The number of CNS events also limits the ability to control for confounding in our study. Lastly, most patients in our cohort presented with COVID-19 which has been independently associated with neurological injury in patients that have not required VV-ECMO.

CONCLUSION

Although rapid decreases in PaCO$_2$ following initiation of VV-ECMO were greater in patients with CNS injuries vs. those without, considerable data overlap and absence of obvious relationships with PaCO$_2$ with brain biomarkers indicates other pathophysiologic variables are at play. NF-L and GFAP were increased in critically ill patients undergoing VV-ECMO for acute respiratory failure in whom we had identified CNS injuries on head CT compared to those without.

Declarations

This manuscript complies with all instructions to authors.

This manuscript has not been published elsewhere and is not under consideration by another journal.

This manuscript assures adherence to ethical guidelines and indicates ethical approvals (IRB) and use of informed consent, as appropriate.

All authors report no Conflict of Interest

Ethical Approval: UBC Clinical Research Ethics Board approval was obtained for the study (H21-00033 / H20-00971) and informed consent was obtained from the patient's legal authorized representative.

Competing interests: None

Authors' contributions: ST, DG were responsible for statistical analysis. ST and MS were responsible data collection. ST, MS and DG were responsible for Figure 1 and 2. SS was responsible for Figure 3. ST, MS and DG wrote the main manuscript text. All authors reviewed the manuscript.

Funding: None

Availability of data and materials: Data available on request
References


15. Cavayas YA, Munshi L, Del Sorbo L, Fan E. The early change in PaCO₂ after extracorporeal membrane oxygenation initiation is associated with neurological complications. Am J Respir Crit


Tables
Table 1
Baseline characteristics of patients prior to VV-ECMO included in the cohort stratified by the absence or presence of central nervous system injury.

<table>
<thead>
<tr>
<th></th>
<th>No-CNS Injury</th>
<th>CNS Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 47</strong></td>
<td></td>
<td>n = 12</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>52 (10)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>8 (17)</td>
<td>3 (25)</td>
</tr>
<tr>
<td><strong>Indication for VV-ECMO, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>40 (85)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>ILD</td>
<td>1 (2)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Post lung transplant</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>ARDS bacterial PNA</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ARDS trauma/inhalation/drug</td>
<td>5 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>INR, mean (SD)</td>
<td>1.2 (0.2)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>PTT, seconds, mean (SD)</td>
<td>41 (41)</td>
<td>62 (48)</td>
</tr>
<tr>
<td>Platelet count x 10^9/L, mean (SD)</td>
<td>232 (111)</td>
<td>184 (137)</td>
</tr>
<tr>
<td>PF pre-VV-ECMO, mean (SD)</td>
<td>74 (20)</td>
<td>66 (18)</td>
</tr>
<tr>
<td>PaCO₂ pre VV-ECMO, mmHg, median [IQR]</td>
<td>67 [54–76]</td>
<td>71 [63–96]</td>
</tr>
<tr>
<td>PaCO₂ post VV-ECMO start, mmHg, median [IQR]</td>
<td>60 [46–84]</td>
<td>67 [61–80]</td>
</tr>
<tr>
<td>PaCO₂ 24-hours post VV-ECMO start, mmHg, median [IQR]</td>
<td>48 [43–56]</td>
<td>50 [45–52]</td>
</tr>
<tr>
<td>PaCO₂ reduction on initiation of VV-ECMO ≥ 27mmHg, n (%)</td>
<td>22 (47)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>ΔPaCO₂ ≥ 50% pre–post% †, n (%)</td>
<td>4 (8)</td>
<td>3 (25)</td>
</tr>
</tbody>
</table>

*CO2 max first 24 hours- CO2 min first 24 hours/Pre-ECMO PaCO₂
†24-h post-ECMO PaCO₂ - pre-ECMO PaCO₂)/pre-ECMO PaCO₂

ARDS Acute Respiratory Distress Syndrome, ECMO Extracorporeal Membrane Oxygenation, ILD interstitial lung disease, MV mechanical ventilation, INR international normalized ratio, IQR interquartile range, mmHg millimeters of mercury, PaCO₂ arterial carbon dioxide partial pressure, SD standard deviation, PF arterial oxygen partial pressure: fraction of inspired oxygen, PNA pneumonia, PTT partial thromboplastin time
<table>
<thead>
<tr>
<th>Comparison</th>
<th>No-CNS Injury</th>
<th>CNS Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 47</td>
<td>n = 12</td>
<td></td>
</tr>
<tr>
<td>(\Delta PaCO_2 \geq 50%_{\text{max-min}})^*</td>
<td>12 (26)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>**, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Delta PaCO_2 %_{\text{max-min}})^*</td>
<td>39 (28–58)</td>
<td>62.5 (47-71.5)</td>
</tr>
</tbody>
</table>

*CO2 max first 24 hours- CO2 min first 24 hours/Pre-ECMO PaCO₂
†24-h post-ECMO PaCO₂ - pre-ECMO PaCO₂)/pre-ECMO PaCO₂

**ARDS** Acute Respiratory Distress Syndrome, **ECMO** Extracorporeal Membrane Oxygenation, **ILD** interstitial lung disease, **MV** mechanical ventilation, **INR** international normalized ratio, **IQR** interquartile range, **mmHg** millimeters of mercury, **PaCO₂** arterial carbon dioxide partial pressure, **SD** standard deviation, **PF** arterial oxygen partial pressure:fraction of inspired oxygen, **PNA** pneumonia, **PTT** partial thromboplastin time

Figures

**Figure 1**
Proposed paradigm for neurological injury on VV-ECMO. During VV-ECMO, venous blood is removed and circulates through a membrane where oxygen is added, and CO$_2$ is removed (A & B). The low CO$_2$ within the cerebral vasculature results in vasoconstriction and decreased cerebral blood flow (C) and the resultant neuronal injury leads to release of neurological biomarkers (GFAP, Tau, NF-L) in the bloodstream.

Figure 2

Arterial carbon dioxide trajectories on VV-ECMO in patients with and without subsequent CNS injury.
Connected line plots of PaCO$_2$ (y-axis) versus time (x-axis) in patients without (left panel) and with (right panel) a CNS injury. Each light grey line is an individual patient. The black line is a predicted curve generated using a restricted cubic splines model.
Neurological biomarker trajectories in the first week following initiation of VV-ECMO in patients with and without subsequent CNS injury. A, B) NF-L C, D) GFAP and E, F) p-tau 181 were quantified in samples taken in the 24h prior to, and 1h, 1d day, and 7d post-initiation of VV-ECMO. Patients were stratified based on the subsequent absence (n=47, no CNS injury graphs A, C, E) or presence (n=12, CNS injury graphs B,
D, F) of CNS injury. Sequential data points within patients are adjoined with a light-colored line, with the dark, thick line representing the group median at each point.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- NCCOnlinesupplementfigures.docx
- NCCOnlinesupplementaltables.docx