ORIGINAL ARTICLE

The Early Change in Pa_{CO_2} after Extracorporeal Membrane Oxygenation Initiation Is Associated with Neurological Complications

Yiorgos Alexandros Cavayas[1,2,3], Laveena Munshi[4], Lorenzo del Sorbo[1], and Eddy Fan[1]

[1]Interdepartmental Division of Critical Care Medicine, Toronto General Hospital, and [4]Interdepartmental Division of Critical Care Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; and [2]Département de Médecine, Hôpital du Sacré-Coeur de Montréal, and [3]Département de Chirurgie, Institut de Cardiologie de Montréal, Université de Montréal, Montreal, Quebec, Canada

ORCID ID: 0000-0001-7664-2104 (Y.A.C.).

Abstract

Rationale: Large decreases in Pa_{CO_2} that occur when initiating extracorporeal membrane oxygenation (ECMO) in patients with respiratory failure may cause cerebral vasoconstriction and compromise brain tissue perfusion.

Objectives: To determine if the magnitude of Pa_{CO_2} correction upon ECMO initiation is associated with an increased incidence of neurological complications in patients with respiratory failure.

Methods: We conducted a multicenter, international, retrospective cohort study using the Extracorporeal Life Support Organization Registry, including adults with respiratory failure receiving ECMO via any mode between 2012 and 2017. The relative change in Pa_{CO_2} in the first 24 hours was calculated as (24-h post-ECMO Pa_{CO_2} − pre-ECMO Pa_{CO_2})/pre-ECMO Pa_{CO_2}. The primary outcome was the occurrence of neurological complications, defined as seizures, ischemic stroke, intracranial hemorrhage, or brain death.

Measurements and Main Results: We included 11,972 patients, 88% of whom were supported with venovenous ECMO. The median relative change in Pa_{CO_2} was −31% (interquartile range, −46% to −12%). Neurological complications were uncommon overall (6.9%), with a low incidence of seizures (1.1%), ischemic stroke (1.9%), intracranial hemorrhage (3.5%), and brain death (1.6%). Patients with a large relative decrease in Pa_{CO_2} (>50%) had an increased incidence of neurological complications compared with those with a smaller decrease (9.8% vs. 6.4%; $P < 0.001$). A large relative decrease in Pa_{CO_2} was independently associated with neurological complications after controlling for previously described risk factors (odds ratio, 1.7; 95% confidence interval, 1.3 to 2.3; $P < 0.001$).

Conclusions: In patients receiving ECMO for respiratory failure, a large relative decrease in Pa_{CO_2} in the first 24 hours after ECMO initiation is independently associated with an increased incidence of neurological complications.

Keywords: extracorporeal membrane oxygenation; neurological complications; carbon dioxide; hypercapnia; stroke

Patients with refractory respiratory failure can be supported with extracorporeal membrane oxygenation (ECMO). The device can take up most of the native lung gas exchange, providing both oxygenation and carbon dioxide (CO_2) clearance. A significant proportion of patients have prominent hypercapnia before ECMO initiation. In the EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) trial, 47% of patients in the ECMO group had a Pa_{CO_2} >55 mm Hg (1). An analysis of the Extracorporeal Life Support Organization (ELSO) Registry suggested that a higher pre-ECMO Pa_{CO_2} was associated with increased mortality in patients receiving ECMO (2). Hypercapnia is likely a marker of underlying disease severity, and, interestingly, the subgroup of patients with severe acute respiratory distress syndrome

(Received in original form January 7, 2020; accepted in final form April 6, 2020)

Supported by a research grant from the Extracorporeal Life Support Organization.

Author Contributions: Conception and design: Y.A.C., L.M., L.d.S., and E.F. Analysis and interpretation: Y.A.C. and E.F. Drafting of the manuscript: Y.A.C. Revision of the manuscript: Y.A.C., L.M., L.d.S., and E.F. All authors agree with the final version.

Correspondence and requests for reprints should be addressed to Eddy Fan, M.D., Ph.D., Interdepartmental Division of Critical Care Medicine, Toronto General Hospital, 585 University Avenue, PMB 11-123, Toronto, ON, M5G 2G2 Canada. E-mail: eddy.fan@uhn.ca.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 201, Iss 12, pp 1525–1535, Jun 15, 2020

Originally Published in Press as DOI: 10.1164/rccm.202001-0023OC on April 6, 2020
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: When treating patients with hypercapnia with extracorporeal membrane oxygenation (ECMO), careful attention to the rate of correction of the Pa_{CO_2} has been advocated. It is believed that large changes in Pa_{CO_2} cause cerebral vasoconstriction and compromise brain tissue perfusion. Indeed, retrospective single-center studies, both in neonates and in adults, have suggested that the magnitude of early correction of Pa_{CO_2} upon initiation of ECMO may be associated with adverse outcomes.

What This Study Adds to the Field: In this large, multicenter, retrospective cohort study including 11,972 patients receiving ECMO for respiratory failure, a greater than 50% decrease in Pa_{CO_2} in the first 24 hours was independently associated with an increased incidence of neurological complications. Although further studies are needed to determine best strategies and optimal correction, modest sweep gas flow rates should be used initially to limit the magnitude of the correction in Pa_{CO_2} in the first 24 hours.

with hypercapnic acidosis experienced the greatest benefit from ECMO in EOLIA (1).

There is a paucity of data on the optimal rate of hypercapnia correction in either invasively or noninvasively ventilated patients. However, given the rapidity with which hypercapnia can be corrected with ECMO, careful attention to the rate of correction of Pa_{CO_2} has been advocated in these patients (3). Indeed, retrospective single-center evidence in both neonates (4) and adults (3) has suggested that the magnitude of correction of Pa_{CO_2} upon initiation of ECMO may be associated with adverse outcomes. Some have hypothesized that a rapid change in Pa_{CO_2} in the first hours of ECMO is paralleled by a similar change in cerebrovascular vasomotor tone resulting in brain hypoxia (5, 6). The rate of Pa_{CO_2} decrease can be controlled by using a very low initial sweep gas flow on the membrane lung and increasing it progressively afterward. Identifying a potentially harmful effect of rapid or large-magnitude hypercapnia correction could lead to easily implemented changes in ECMO patient management. Therefore, our primary objective in the present study was to determine if the magnitude of Pa_{CO_2} correction in the first 24 hours of ECMO initiation is associated with an increased incidence of neurological complications in a large multicenter cohort of patients with respiratory failure. In addition, we wanted to evaluate the association between Pa_{CO_2} correction and mortality.

Methods

Study Design

We conducted a multicenter retrospective cohort study using a limited, deidentified data set from the ELSO Registry. The ELSO Registry compiles data on ECMO use from more than 400 international centers after approval by local institutional review boards. For each ECMO run, participating centers fill out a standardized case report form containing patient demographics, diagnosis, and procedure information; ECMO technique; physiological and microbiological data; complications; and outcomes (online supplement). ELSO releases limited data sets to participating centers for research purposes, without any patient or hospital identifying information. We extracted data on all adult patients (>18 yr) who received ECMO primarily for respiratory failure between January 2012 and December 2017. All ECMO modalities were included: venovenous, venoarterial, or hybrid. If the patients had multiple episodes of ECMO, only data from the first episode were used for analyses. This study was approved by the research ethics board of the University Health Network (Toronto, ON, Canada; 18-5183).

Principle Variable of Interest

The ELSO Registry collects arterial blood gas (ABG) values before initiation of ECMO and 24 hours after the initiation of ECMO. The absolute early change in Pa_{CO_2} upon ECMO initiation ($Abs\Delta CO_2$) was calculated using the following formula:

$$Abs\Delta CO_2 = \text{post-ECMO } Pa_{CO_2} - \text{pre-ECMO } Pa_{CO_2}.$$

To minimize the influence of the pre-ECMO Pa_{CO_2} in our measurement of early change, we chose *a priori* to use the relative early change in Pa_{CO_2} ($Rel\Delta CO_2$) as our main variable of interest. It was calculated using the following formula:

$$Rel\Delta CO_2 = Abs\Delta CO_2 / \text{pre-ECMO } PaCO_2.$$

Covariates

The pre-ECMO variables included demographic variables, diagnosis, cardiac arrest, ABG, ventilator settings, and pre-ECMO rescue therapies. International Classification of Diseases, Ninth Revision, diagnosis codes were translated into the diagnostic categories used in the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score (2): "bacterial pneumonia," "viral pneumonia," "aspiration pneumonitis," "asthma," "trauma/burn," and "other acute respiratory diagnoses." "Renal dysfunction" included chronic or acute renal insufficiency (e.g., creatinine >1.5 mg/dl) with or without renal replacement therapy. Similarly, "heart dysfunction" was defined by chronic or acute heart failure. "Acute associated infection" was defined as a bacterial, viral, parasitic, or fungal infection that did not involve the lung (e.g., intraabdominal sepsis). "Immunocompromised" was defined as hematologic malignancies, solid tumor, solid organ transplant, HIV, or cirrhosis. ECMO modes were reported as venoarterial or venovenous, including dual-lumen cannula, hybrid modes, or conversions from one mode to another.

Outcome

ELSO collects data on the occurrence of the following neurological complications: clinical brain death, clinical seizures, EEG-proven seizures, central nervous system infarction, and central nervous system hemorrhage. The primary outcome was neurological complications, a composite outcome defined as the occurrence of any of the aforementioned complications. The secondary outcome was ICU mortality. Moreover, for the purpose of our study, seizures were defined as the occurrence of clinical seizures or EEG-proven seizures.

Statistical Analysis

The extracted database was thoroughly inspected and cleaned. All physiologically implausible ABG values were assessed for possible entry in kilopascals (kPa) instead of millimeters of mercury (mm Hg) by using an algorithm to calculate the pH according

to the Henderson-Hasselbalch equation with the entered bicarbonates and the Pa_{CO_2} as kPa. If the calculated pH corresponded to the pH entered in the database, the Pa_{CO_2} and Pa_{O_2} values were converted to mm Hg by multiplying them by 7.5. All values of continuous variables that were not physiologically possible were excluded (treated as missing). Continuous variables are presented as medians with interquartile ranges (IQR). Categorical variables are presented as counts and percentages. We plotted the incidence of neurological complications according to intervals of $Rel\Delta CO_2$ to evaluate the nature of the relationship (i.e., linear or nonlinear) between the two variables. We also compared the incidence of individual neurological complications across different intervals of $Rel\Delta CO_2$ using Pearson's chi-squared test. To assess if $Rel\Delta CO_2$ was independently associated with the incidence of neurological complications, we performed a multivariable logistic regression by entering $Rel\Delta CO_2$ (as a categorical variable) with the variables found to be associated with neurological complications in an earlier analysis of the ELSO Registry (7): pre-ECMO cardiac arrest, hyperbilirubinemia, and the use of renal replacement therapy. We performed a sensitivity analysis in which age and pre-ECMO Pa_{CO_2} were entered in the multivariable logistic regression as well. We tested for interaction between pre-ECMO Pa_{CO_2} and $Rel\Delta CO_2$. The primary analysis was performed by excluding cases with missing variables for the primary analysis. A sensitivity analysis with a multiple imputation model was also performed. Moreover, sensitivity analyses with $Abs\Delta CO_2$ instead of $Rel\Delta CO_2$ or age and baseline Pa_{CO_2} entered in the model are also presented. To assess if $Rel\Delta CO_2$ was independently associated with mortality, we also conducted a multivariable logistic regression in which $Rel\Delta CO_2$ was entered with the RESP score variables established by an earlier analysis of the same registry (2). All of these analyses were planned *a priori*.

Multiple *post hoc* sensitivity and exploratory analyses were performed as well. First, baseline acid–base status entered into the model was added. The relationship between $Rel\Delta CO_2$ and the incidence of neurological complications was also assessed across different subgroups of patients likely to have been exposed to prolonged periods of hypercapnia: patients with chronic obstructive pulmonary disease (COPD), those with interstitial lung disease, patients with lung transplant, and patients with prolonged mechanical ventilation (defined as invasive mechanical ventilation [IMV] duration >7 d preceding ECMO

Table 1. Baseline Characteristics

Parameter	Overall (*N* = *11,972*)	Relative Pa_{CO_2} Drop <50% (*n* = *7,155*)	Relative Pa_{CO_2} Drop >50% (*n* = *1,719*)
Age, yr	48 (35–60)	48 (35–59)	46 (32–58)
Sex, M	6,968 (58%)	4,315 (61%)	1,010 (59%)
Weight, kg	81 (68–100)	82 (69–100)	80 (65–96)
Diagnostic category			
Viral pneumonia	1,776 (16%)	1,159 (17%)	195 (12%)
Bacterial pneumonia	1,345 (12%)	845 (13%)	172 (11%)
Asthma	388 (4%)	152 (2%)	179 (11%)
Trauma/burns	603 (6%)	418 (6%)	89 (6%)
Aspiration pneumonitis	259 (2%)	152 (2%)	47 (3%)
Chronic lung disease	306 (3%)	177 (3%)	61 (4%)
Other acute lung disease	4,815 (44%)	2,965 (44%)	679 (42%)
Nonrespiratory disease	1,552 (14%)	869 (13%)	180 (11%)
Immunocompromised	1,500 (13%)	926 (13%)	210 (12%)
Respiratory function			
Respiratory rate, breaths/min	22 (18–30)	22 (17–28)	24 (18–30)
Peak inspiratory pressure, cm H_2O	34 (30–38)	33.6 (29–38)	35 (30–40)
Positive end-expiratory pressure, cm H_2O	12 (10–16)	13 (10–16)	12 (8–15)
Pa_{O_2}/FI_{O_2} ratio	65 (52–87)	64 (52–86)	71 (53–103)
Oxygenation index, cm H_2O/mm Hg	34 (24–47)	34 (24–47)	33 (21–46)
Baseline Pa_{CO_2}, mm Hg	59 (47–75)	54 (44–65)	92 (78–112)
Support			
High-frequency ventilation	361 (2%)	175 (3%)	32 (2%)
Nitric oxide	1,294 (11%)	968 (14%)	173 (10%)
Neuromuscular blockade	3,394 (28%)	2,286 (32%)	599 (35%)
Bicarbonate infusion	778 (7%)	482 (7%)	161 (9%)
Pre-ECMO arrest	995 (9%)	512 (7%)	207 (12%)
Nonrespiratory infection	1,370 (12%)	5,883 (87%)	1,398 (87%)
ECMO mode			
Venovenous	10,510 (88%)	6,369 (89%)	1,556 (91%)
Venoarterial	851 (7%)	445 (6%)	95 (6%)
Conversion	341 (3%)	212 (3%)	37 (2%)
Hybrid	111 (1%)	65 (1%)	14 (1%)
Duration of IMV before ECMO, h	34 (9–109)	40 (12–115)	25 (8–102)

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; IMV = invasive mechanical ventilation.
Data are presented as median (interquartile range) or *n* (%).

initiation) or ABG values compatible with chronic hypercapnia. Hypercapnic acidosis was defined as a pH lower than 7.30 with a Pa_{CO_2} >50 mm Hg. Acute hypercapnia was defined as hypercapnic acidosis with <2 mEq of bicarbonate increase per 10 mm Hg of Pa_{CO_2} increase, whereas chronic hypercapnia was defined by the presence of >2 mEq of bicarbonate compensation per 10 mm Hg of Pa_{CO_2} increase. The Breslow-Day test was used to assess homogeneity across subgroups, and the Mantel-Haenszel test was used to assess overall significance. Finally, the adjusted odds ratio (OR) for the association between $Rel\Delta CO_2$ and neurological complications across different age groups and ECMO mode was assessed by performing stratified logistic regression models. We also explored if oxygenation variables (pre-ECMO Pa_{O_2}, post-ECMO Pa_{O_2}, $Abs\Delta O_2$, and $Rel\Delta O_2$) were associated with neurological complications and, if so, if the association between $Rel\Delta CO_2$ and neurological complications remained significant once oxygenation variables were entered in the multiple logistic regression model. The details of this analysis can be found in the online supplement. All analyses were performed using IBM SPSS Statistics version 25.0 software (IBM Corp.) and Python 3.6.5 software (Python Software Foundation; www.python.org).

Results

During the study period, there were 12,177 episodes of ECMO support for respiratory failure in 11,972 adult patients entered in the ELSO Registry. Only first episodes were included in the analyses. The baseline characteristics of the patients can be found in Table 1. The majority (88%) of patients were supported with venovenous ECMO exclusively, with the remainder being supported with venoarterial ECMO, hybrid modes, or more than one mode because of conversions. Severe hypoxemia (Pa_{O_2}/FI_{O_2} <100) (8) was present in 84% of cases, and hypercapnic acidosis (pH <7.3 with Pa_{CO_2} >50) (9, 10) was present in 54% of cases. Critical hypoxemia (Pa_{O_2}/FI_{O_2} <50) and hypercapnic acidosis (pH <7.25 with Pa_{CO_2} >60) (1) were present at baseline in 21% and 35% of patients, respectively. The median absolute early change in Pa_{CO_2} was −18 mm Hg (IQR, −33 to −6 mm Hg). This translated to a median $Rel\Delta CO_2$ of −31% (IQR, −46% to −12%). The histograms of the distribution can be found in Figure 1. At least one of the two Pa_{CO_2} values was missing in 3,098 cases (26%).

The primary composite outcome of neurological complications occurred in 6.9%, including seizures (1.1%), ischemic stroke (1.9%), intracranial hemorrhage (3.5%), and brain death (1.6%). The overall ICU mortality was 39.7% (Table 2). We found a U-shaped relationship between the $Rel\Delta CO_2$ and the incidence of neurological complications (Figures 2 and 3). Patients with a relative Pa_{CO_2} drop >50% had a significantly increased incidence of neurological complications compared with patients with a relative Pa_{CO_2} drop <50% (9.8% vs. 6.4%; $P < 0.001$). A relative Pa_{CO_2} drop <50% was documented in 1,719 patients (19%). The baseline characteristics of this subgroup can be contrasted with those of the rest of the patients in Table 1. Apart from the expected difference in baseline Pa_{CO_2}, we found more patients with pre-ECMO cardiac arrest in the group of patients with the largest decrease in relative Pa_{CO_2}. The association between the

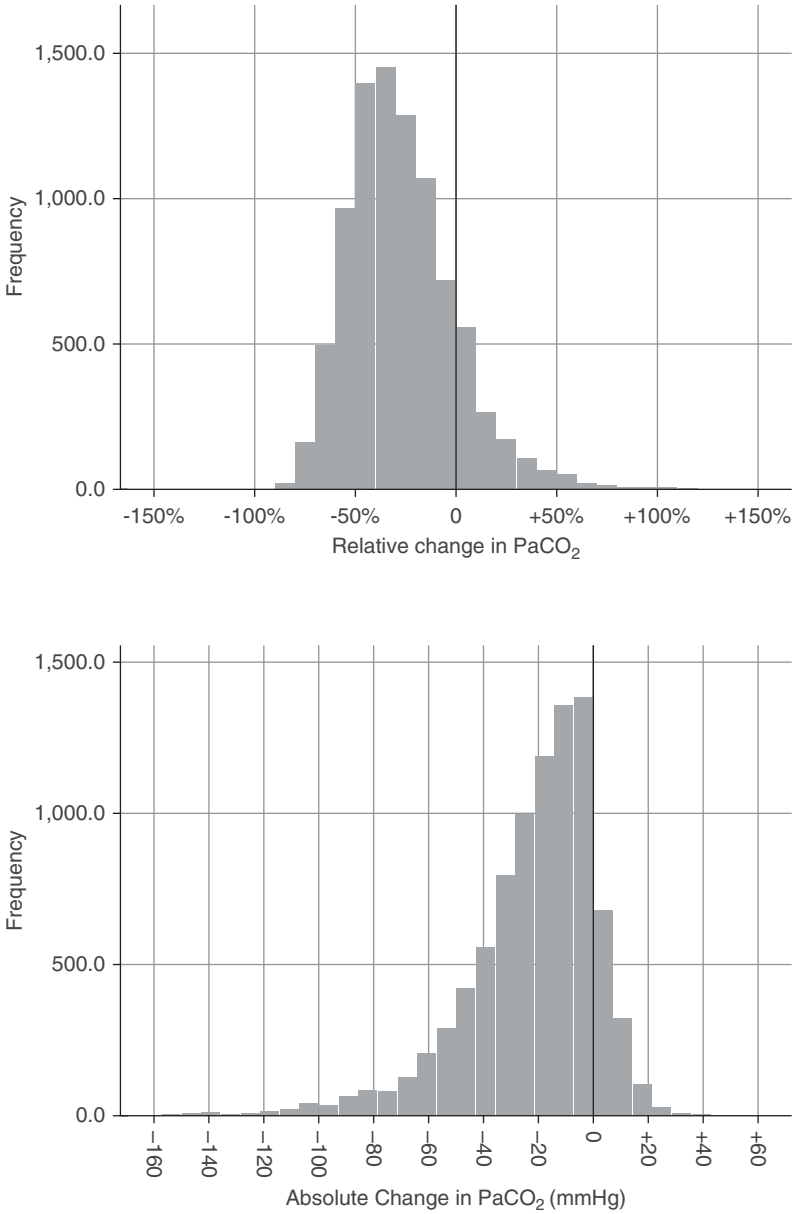

Figure 1. Distribution of the absolute and relative changes in Pa_{CO_2} in the first 24 hours after extracorporeal membrane oxygenation initiation.

Table 2. Outcomes

Outcome	Overall		Relative Pa_{CO_2} Drop <50%		Relative Pa_{CO_2} Drop >50%		Chi-Squared Test *P* Value
	n	%	*n*	%	*n*	%	
Seizure	137	1.1%	80	1.1%	33	1.9%	0.008
Ischemic stroke	223	1.9%	124	1.7%	39	2.3%	0.137
Intracranial hemorrhage	415	3.5%	238	3.3%	79	4.6%	0.011
Brain death	186	1.6%	96	1.3%	48	2.8%	<0.001
Neurological complications	832	6.9%	459	6.4%	168	9.8%	<0.001
ICU mortality	4,721	39.7%	2,735	38.6%	709	41.5%	0.030

$Rel\Delta CO_2$ and the incidence of neurological complications, however, remained significant when we controlled for pre-ECMO cardiac arrest together with the other two previously described risk factors for neurological complications (hyperbilirubinemia and renal replacement therapy) (7) (Table 3).

This was also the case when we entered age, baseline Pa_{CO_2}, baseline acid–base status, and oxygenation variables in the model. Age and baseline Pa_{CO_2} were not significantly associated with the incidence of neurological complications, but the baseline acid–base status and oxygenation variables were (*see* online supplement). More specifically, baseline metabolic acidosis was associated with an increased risk of neurological complications (OR, 1.50; 95% confidence interval [CI], 1.08–2.09). Post-ECMO hypoxemia (Pa_{O_2} <60 mm Hg) and severe hyperoxemia (Pa_{O_2} >300 mm Hg) were also associated with an increased incidence of neurological complications (OR, 1.31 [95% CI, 1.06–1.62]; and OR, 1.62 [95% CI, 1.08–2.43], respectively). There was no significant interaction between baseline Pa_{CO_2} and $Rel\Delta CO_2$. The association between $Rel\Delta CO_2$ and the incidence of neurological complications remained significant when multiple imputations were used to estimate the missing values (Table 4). The increase in the risk of neurological complications associated with a relative Pa_{CO_2} drop >50% was significantly greater in patients with a longer pre-ECMO duration of IMV (>7 d) than in those with a shorter duration (<7 d) (OR, 2.87 [95% CI, 1.91–4.20] vs. 1.33 [95% CI, 1.06–1.66]; $P = 0.001$). A similar but nonsignificant trend was observed in patients with COPD compared with those without COPD (OR, 3.38 [95% CI, 1.27–8.98] vs. 1.54 [95% CI, 1.27–1.86]; $P = 0.114$). Other tested subgroups were homogeneous (Figure 3). The association between relative Pa_{CO_2} drop >50% and neurological complications was similar across age groups and ECMO modes (Figure 4). A high $AbsCO_2$ was also strongly and independently associated with an increased incidence of neurological complications (Table 5). Finally, a relative Pa_{CO_2} drop >50% was associated with increased ICU mortality in unadjusted analysis (41.5% vs. 38.6%; $P = 0.03$). However, this association was no longer significant after adjusting for the RESP score variables (Table 6).

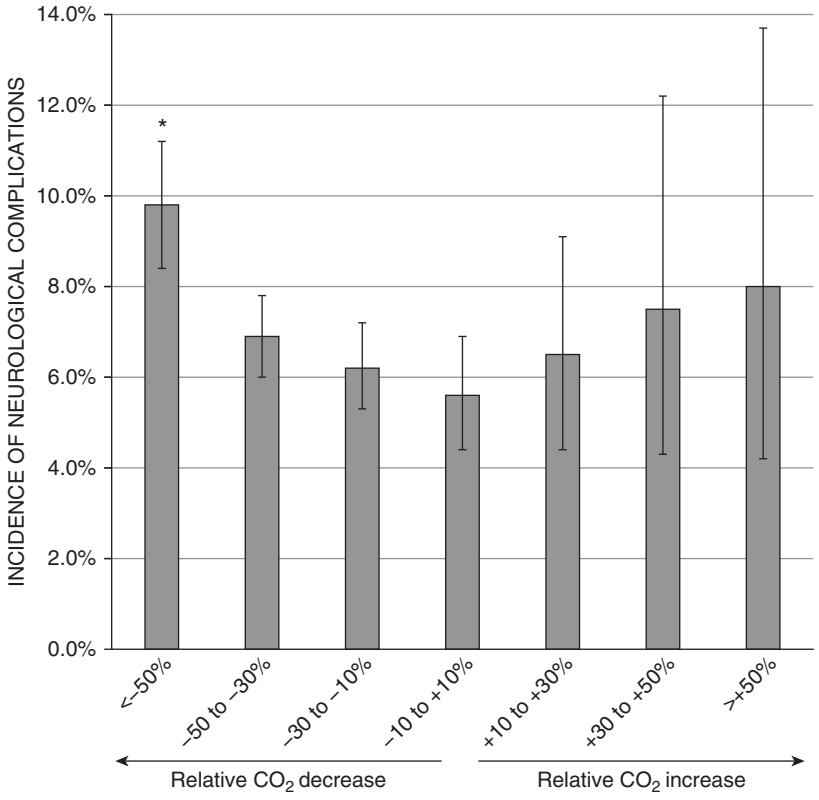

Figure 2. Incidence of neurological complications according to $Rel\Delta CO_2$ interval. *Significant difference in the incidence of neurological complications between the subgroup of patients with the highest relative decrease in Pa_{CO_2} (relative Pa_{CO_2} drop > 50%) and those with a minimal change (−10% to +10%). Error bars represent 95% confidence intervals. $Rel\Delta CO_2$ = relative change in Pa_{CO_2} upon extracorporeal membrane oxygenation initiation.

Discussion

In this cohort of 11,972 patients who received ECMO for respiratory failure, we found that the $Rel\Delta CO_2$ upon ECMO

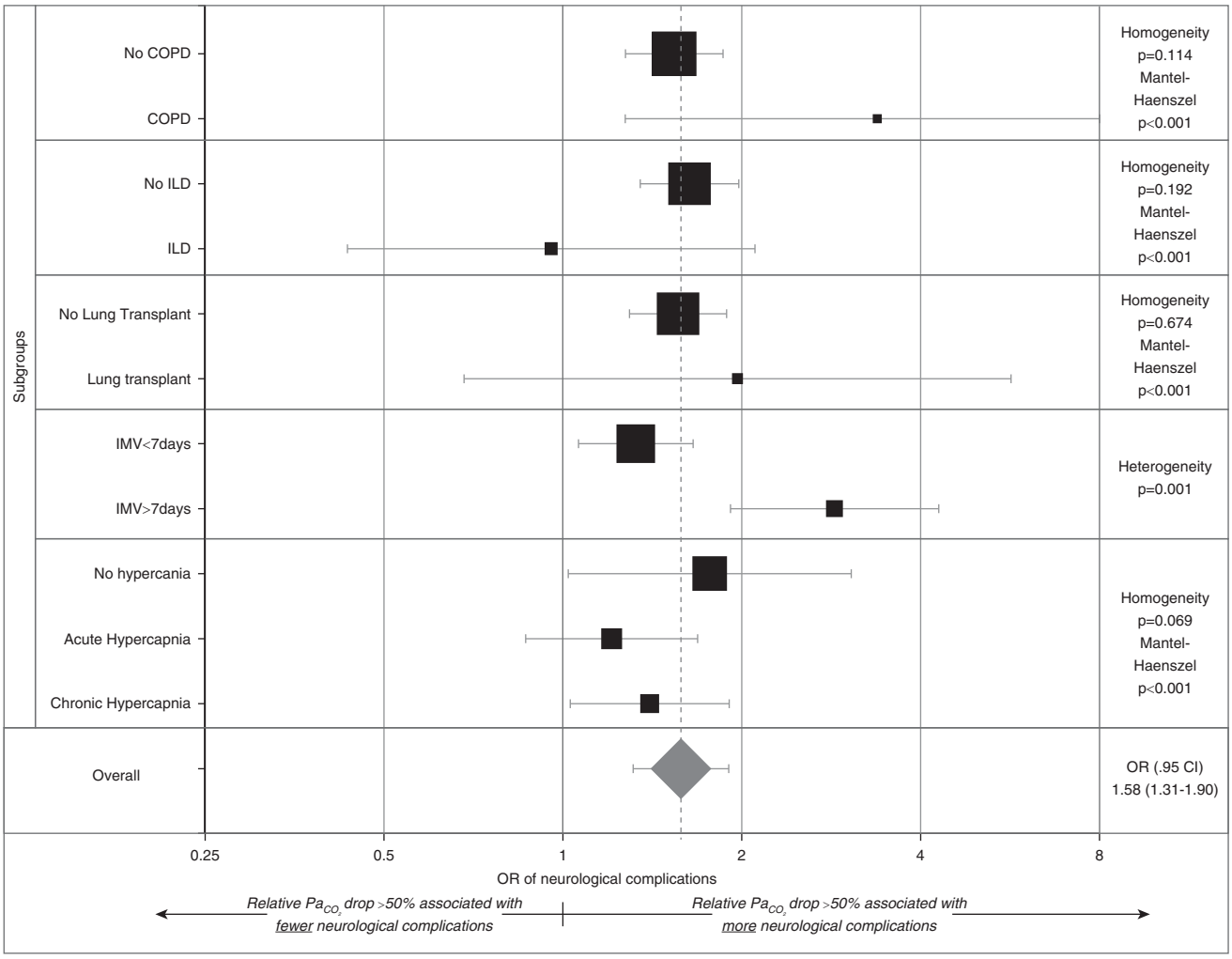

Figure 3. Association of a relative Pa_{CO_2} drop greater than 50% with neurological complications (unadjusted odds ratio [OR]) across different subgroups likely to have been exposed to hypercapnia for prolonged periods. Exploratory analysis was performed to assess the relationship between RelΔCO_2 and the incidence of neurological complications across different subgroups of patients likely to have been exposed to prolonged periods of hypercapnia. Hypercapnic acidosis was defined as a pH less than 7.30 with a Pa_{CO_2} >50 mm Hg. Acute hypercapnia was defined as hypercapnic acidosis with <2 mEq of base excess per 10 mm Hg of Pa_{CO_2} increase, whereas chronic hypercapnia was defined by the presence of >2 mEq of bicarbonate compensation per 10 mm Hg of Pa_{CO_2} increase. The Breslow-Day test was used to assess homogeneity across subgroups, and the Mantel-Haenszel test was used to assess overall significance. Error bars represent 95% confidence intervals. CI = confidence interval; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; IMV = invasive mechanical ventilation (duration before extracorporeal membrane oxygenation [ECMO] initiation); RelΔCO_2 = relative change in Pa_{CO_2} upon ECMO initiation.

initiation was associated with a significantly increased incidence of neurological complications. The RelΔCO_2 was not, however, associated with the risk of death when controlling for previously described prognostic factors. Our data suggest that clinicians should monitor the ABGs frequently and use modest sweep gas flow rates initially to limit the magnitude of the correction in Pa_{CO_2} in the first 24 hours to prevent neurological complications in patients with respiratory failure supported with ECMO.

The association we observed between RelΔCO_2 and neurological complications has strong biological plausibility. Both hypercapnia and hypocapnia have generally been associated with worse outcomes in patients with neurological injury (11), because cerebral vascular tone is highly sensitive to changes in Pa_{CO_2} (12). Hypercapnia results in vasodilation, which can increase cerebral blood flow (13) that could result in hyperperfusion (14) and cerebral edema (15, 16). Moreover, a global vasodilatory stimulus such as hypercapnia could cause a "steal" phenomenon whereby regions with less vasodilatory reserve become hypoperfused, resulting in focal ischemia (17). Decreases in Pa_{CO_2} cause dose-dependent vasoconstriction (13), with a resulting fall in cerebral blood flow of as much as 3% per 1-mm Hg change in Pa_{CO_2} (when going from 60 to 20 mm Hg) (18). This may directly compromise brain perfusion and cause ischemia (19). Hypocapnia also increases the affinity of hemoglobin for oxygen, further compromising oxygen delivery. A low Pa_{CO_2} increases neuronal excitability (20) that can trigger seizures (21) or prolong

Table 3. Multiple Logistic Regression Assessing Association between RelΔCO_2 and Neurological Complications When Controlling for Previously Described Risk Factors ($n = 8,760$)

Variables	OR	95% CI for OR		*P* Value
		Lower Bound	Upper Bound	
Pre-ECMO cardiac arrest	2.394	1.909	3.003	<0.001
Hyperbilirubinemia	2.130	1.693	2.679	<0.001
Renal replacement therapy	1.403	1.179	1.670	<0.001
RelΔCO_2	—	—	—	0.002
<−50%	1.732	1.295	2.317	<0.001
−50% to −30%	1.199	0.904	1.592	0.208
−30% to −10%	1.100	0.820	1.477	0.524
−10% to +10%		Reference		
+10% to +30%	1.143	0.725	1.803	0.565
+30% to +50%	1.304	0.701	2.425	0.402
>+50%	1.394	0.695	2.795	0.349

Definition of abbreviations: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio; RelΔCO_2 = relative change in Pa_{CO_2} upon ECMO initiation.

them (22). This increases the central nervous system metabolic rate (23). Hypocapnia thus results in an imbalance between decreased oxygen delivery and increased oxygen demand (24) and may augment brain tissue ischemia and reperfusion injury (25).

Patients supported with ECMO have preserved cerebrovascular reactivity (26). Although associated with an increase in Pa_{O_2}, initiation of venovenous ECMO in patients with respiratory failure has been shown to be associated with a significant drop in regional brain tissue oxygen saturation as measured by near-infrared spectroscopy (5, 6). This drop correlated with the drop in Pa_{CO_2} in patients without hypoxemia (5). Patients with hypercapnic respiratory failure sustained for more than a few hours have an increase in cerebrospinal fluid (CSF) bicarbonate concentration that reaches a maximum by 24 hours and partly restores the CSF pH (27). Sudden correction of Pa_{CO_2} to the normal range, which may occur with ECMO initiation, acutely alkalinizes the CSF as hypocapnia would in a healthy individual, with resulting vasoconstriction (Figure 5). In our study, patients with a longer duration of IMV, possibly exposed to hypercapnia for a longer period, appeared more sensitive to the deleterious effects of a large RelΔCO_2. There was a similar nonsignificant trend in patients with COPD. Some studies have suggested that patients chronically exposed to hypercapnia, such as those with obstructive sleep apnea, may have increased cerebral vascular reactivity (28). This could render them more sensitive to subsequent drastic decreases in Pa_{CO_2} with ECMO initiation.

Table 4. Sensitivity Analyses for Association of Relative Change in Pa_{CO_2} upon Extracorporeal Membrane Oxygenation Initiation with Neurological Complications

Variables	OR	95% CI for OR		*P* Value
		Lower Bound	Upper Bound	
Analysis with age and baseline Pa_{CO_2} without interaction ($n = 8,730$)*				
Age	0.996	0.991	1.002	0.197
Baseline Pa_{CO_2}	1.002	0.998	1.006	0.314
Relative Pa_{CO_2} drop > 50%	1.399	1.095	1.788	0.007
Analysis with age, baseline Pa_{CO_2}, and interaction ($n = 8,730$)*				
Age	0.996	0.991	1.002	0.200
Baseline Pa_{CO_2}	1.003	0.997	1.009	0.289
(Baseline Pa_{CO_2}) × (relative Pa_{CO_2} drop > 50%)	0.998	0.990	1.006	0.617
Relative Pa_{CO_2} drop > 50%	1.622	0.866	3.039	0.131
Analysis with baseline acid–base status ($n = 8,723$)*				
Relative Pa_{CO_2} drop > 50%	1.444	1.188	1.755	<0.001
Baseline acid–base status	—	—	—	0.022
Normal pH			Reference	
Alkalosis, respiratory	0.949	0.505	1.784	0.872
Alkalosis, metabolic	0.249	0.060	1.025	0.054
Acidosis, respiratory	1.238	0.949	1.614	0.115
Analysis with multiple imputation ($N = 11,972$)				
Pre-ECMO cardiac arrest	2.417	1.928	3.029	<0.001
Hyperbilirubinemia	2.145	1.708	2.693	<0.001
Renal replacement therapy	1.403	1.180	1.669	<0.001
Relative Pa_{CO_2} drop > 50%	1.542	1.278	1.860	<0.001

Definition of abbreviations: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio.
*Pre-ECMO cardiac arrest, hyperbilirubinemia, and renal replacement therapy were entered in the model and found to be statistically significant ($P < 0.001$), but they are not shown.

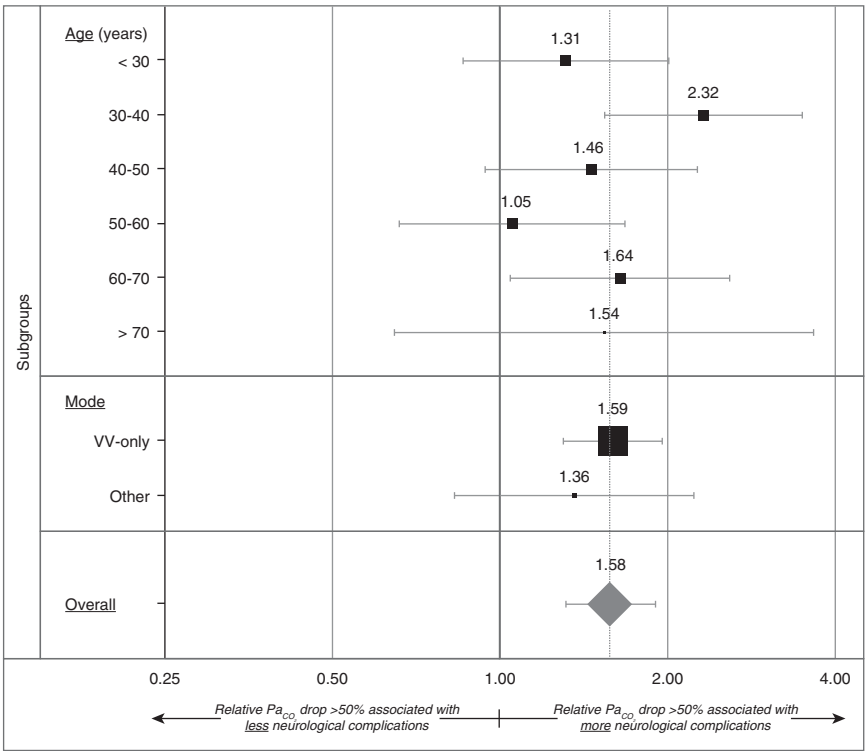

Figure 4. Association of a relative Pa_{CO_2} drop >50% with neurological complications (adjusted odds ratio) across other age groups and extracorporeal membrane oxygenation (ECMO) mode. Exploratory analysis was performed to assess the relationship between RelΔCO_2 and the incidence of neurological complications across different age groups and ECMO modes, adjusted for hyperbilirubinemia, renal replacement therapy, and pre-ECMO cardiac arrest. Error bars represent 95% confidence intervals. RelΔCO_2 = relative change in Pa_{CO_2} upon ECMO initiation; VV = venovenous.

The brain tissue ischemia caused by the vasoconstriction accompanying acute correction of the Pa_{CO_2} may be at the heart of its association with neurological complications. A similar relationship has been observed in previous smaller studies, both in adults receiving venovenous ECMO (3) and venoarterial ECMO (29) and in children (4). Patients with respiratory failure who are receiving ECMO are a very sick group that may be particularly sensitive to the deleterious effects of rapid or large changes in Pa_{CO_2} or Pa_{O_2} because of a complex interplay of disease- and treatment-related factors (30). The initiation of ECMO is a critical period in which multiple elements coincide. During cannulation, patients have to lie flat in a supine position, which may temporarily worsen gas exchange and increase intracranial pressure. Then, they are usually given a bolus of heparin, which puts them at high risk of bleeding. Large cannulas are often inserted into the right internal jugular vein with the potential of causing cerebral venous congestion (31). When the extracorporeal support is started, blood comes into contact with the circuit. This activates inflammatory and coagulation pathways with potential impacts on the development of thromboembolic or hemorrhagic complications. Interestingly, however, recent studies found similar rates of intracranial hemorrhage in patients with severe acute respiratory failure, with or without ECMO (1, 32), suggesting that disease-related factors may be more important than ECMO-related factors. The 6.9% rate of neurological complications we found in our study is relatively low compared with the median rate of 13% found in a recent systematic review and meta-analysis (33). This could suggest that ECMO-related factors were minimized over time with improvements in technology and clinician experience. Our findings, however, suggest that complications may be further mitigated by preventing large, rapid shifts in Pa_{CO_2} and avoiding hypoxemia and severe hyperoxemia.

Table 5. Sensitivity Analyses for Association of Absolute Early Change in Pa_{CO_2} upon Extracorporeal Membrane Oxygenation Initiation with Neurological Complications (n = 8,760)

Variables	OR	95% CI for OR		*P* Value
		Lower Bound	Upper Bound	
Pre-ECMO cardiac arrest	2.431	1.939	3.048	<0.001
Hyperbilirubinemia	2.143	1.703	2.696	<0.001
Renal replacement therapy	1.411	1.185	1.68	<0.001
AbsΔCO_2	—	—	—	0.001
<−60 mm Hg	1.957	1.395	2.747	<0.001
−60 to −40 mm Hg	1.548	1.127	2.126	0.007
−40 to −20 mm Hg	1.132	0.857	1.496	0.381
−20 to −5 mm Hg	1.141	0.868	1.499	0.345
−5 to +5 mm Hg		Reference		
+5 to +20 mm Hg	1.069	0.707	1.617	0.751
>+20 mm Hg	1.863	0.766	4.530	0.170

Definition of abbreviations: AbsΔCO_2 = absolute early change in Pa_{CO_2} upon ECMO initiation; CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio.

Our study represents the largest cohort of patients with respiratory failure used to evaluate the relationship between early changes in Pa_{CO_2} and the occurrence of neurological complications. Although our study cannot prove causality, there are a number of findings that support a causal association between early changes in Pa_{CO_2} and neurological complications (34). First, the magnitude of the association is strong (adjusted OR, 1.732; $P < 0.001$). Second, it is consistent across a number of sensitivity analyses and with the results of other studies in different populations (3, 4, 29). Third, there is a dose–response relationship in both directions of change in Pa_{CO_2} (Figure 2). Finally, there are many well-documented physiological mechanisms by which early changes in Pa_{CO_2} may result in

Table 6. Multiple Logistic Regression Assessing Association between Relative Change in Pa_{CO_2} upon Extracorporeal Membrane Oxygenation Initiation and Survival ($n = 5,604$)

Variables	OR	95%CI Lower Bound	95% CI Upper Bound	*P* Value
Age	0.973	0.970	0.977	<0.001
Immunocompromised	0.454	0.385	0.534	<0.001
Time on mechanical ventilation	0.999	0.998	0.999	<0.001
Diagnostic category				<0.001
Viral pneumonia	1.08	0.878	1.330	0.465
Bacterial pneumonia	2.686	1.821	3.960	<0.001
Asthma	1.11	0.849	1.452	0.446
Trauma/burns	1.458	0.977	2.176	0.065
Aspiration pneumonitis	1.073	0.737	1.561	0.713
Chronic lung disease	0.902	0.764	1.066	0.228
Other acute lung disease	0.862	0.693	1.073	0.184
Nonrespiratory disease	0.716	0.604	0.848	<0.001
Neuromuscular blockers	1.173	1.039	1.324	0.010
Nitric oxide	0.935	0.792	1.103	0.424
Bicarbonate infusion	0.802	0.654	0.983	0.034
Peak inspiratory pressure	0.986	0.981	0.992	<0.001
Pre-ECMO cardiac arrest	0.649	0.525	0.803	<0.001
Baseline Pa_{CO_2}	0.997	0.993	1.000	0.048
RelΔCO_2	—	—	—	0.145
<−50%	0.980	0.755	1.272	0.881
−50% to −30%	0.943	0.774	1.149	0.56
−30% to −10%	1.112	0.919	1.345	0.275
−10% to +10%		Reference		
+10% to +30%	1.107	0.814	1.507	0.516
+30% to +50%	0.682	0.441	1.056	0.086
>+50%	0.802	0.483	1.334	0.396

Definition of abbreviations: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio; RelΔCO_2 = relative change in Pa_{CO_2} upon ECMO initiation; RESP = Respiratory Extracorporeal Membrane Oxygenation Survival Prediction.
We controlled for the RESP score variables.

neurological complications, as detailed previously. Thus, our findings have important implications for the management of patients with respiratory failure who are being supported with ECMO. Although further studies are needed to determine the best strategies and optimal correction targets, it may be appropriate to monitor ABGs frequently and to use low sweep gas flows initially to limit the correction of Pa_{CO_2} in the first 24 hours (3). Noninvasive neuromonitoring such as near-infrared spectroscopy (5) or transcranial Doppler ultrasonography could be used to avoid harmful vasoconstriction. Such a strategy could result in a reduction of neurological complications and requires confirmation in future studies.

Our study has a number of important limitations. First, given the nonexperimental design of this study, there is both residual and unmeasured confounding. For instance, the ELSO Registry did not collect data such as platelet counts and coagulation tests. Second, only two ABGs per patient were available. Averaging the absolute change in Pa_{CO_2} associated with an increased incidence of neurological complication over a 24-hour period would suggest that a drop >2 mm Hg/h may be deleterious. Targeting a correction rate below that threshold could represent a conservative approach to mitigate the development of neurological complications. This, however, could be an overly stringent target. Markedly different Pa_{CO_2} kinetics with probably markedly different physiological effects on brain perfusion may produce similar 24-hour changes in Pa_{CO_2}. The same change in Pa_{CO_2} may be produced by a slow and steady decline over 24 hours but also by a fast drop with subsequent stabilization or even a very deep drop with subsequent reincrease. Because ABG composition can change very quickly, the Pa_{CO_2} value reported may not even be representative of the day's average and may just represent a very transient state. One may easily conceive of 5 minutes of hypocapnia probably not having the same effect as 5 hours of hypocapnia. Although this phenomenon may introduce some imprecision in the estimation of the general trend of change in Pa_{CO_2}, it is unlikely that it introduces a systematic bias resulting in an overestimation of the effect. Data with greater granularity are needed to provide more accurate guidance on Pa_{CO_2} correction targets. Third, missing ABG values may limit the internal validity of our study. We attempted to address this problem through multiple imputation, which was used in a sensitivity analysis. Moreover, it is highly unlikely that any patient receiving ECMO did not have any ABG tests performed in the 24 hours before and after ECMO initiation. Therefore, missing values most likely represent nonentry in the database rather than nonmeasurement of ABGs. The distinction is important because nonentry most likely represents data that are missing at random, as compared with a more systematic reason for missingness. Fourth, the increased incidence of neurological complications with an increase in Pa_{CO_2} should be interpreted with caution. A relatively small number of patients ($n = 730$; 8% of all patients) experienced an increase in Pa_{CO_2}. The increase in Pa_{CO_2} despite ECMO can be explained physiologically in the majority of these patients. In 295 patients, pH increased despite the increase in Pa_{CO_2}, suggesting a respiratory compensation for an increase in bicarbonate. Another 153 patients had baseline respiratory alkalosis that improved over the first 24 hours. As for the rest of the patients, the increase in Pa_{CO_2} may be a sign of poorly functioning or nonfunctioning extracorporeal support. Finally, the use of a large international multicenter cohort of patients with very wide inclusion criteria gives our study excellent external validity for the population of patients with respiratory failure receiving ECMO. However, whether large changes in Pa_{CO_2} have the same impact on patients with respiratory failure receiving low-flow extracorporeal CO_2 removal or on conventionally ventilated patients should be further studied. Although the same injurious physiological changes probably occur in other patients, there may be important differences in other contributing factors previously alluded to (e.g., anticoagulation, blood–circuit interaction) in the other critically ill patients.

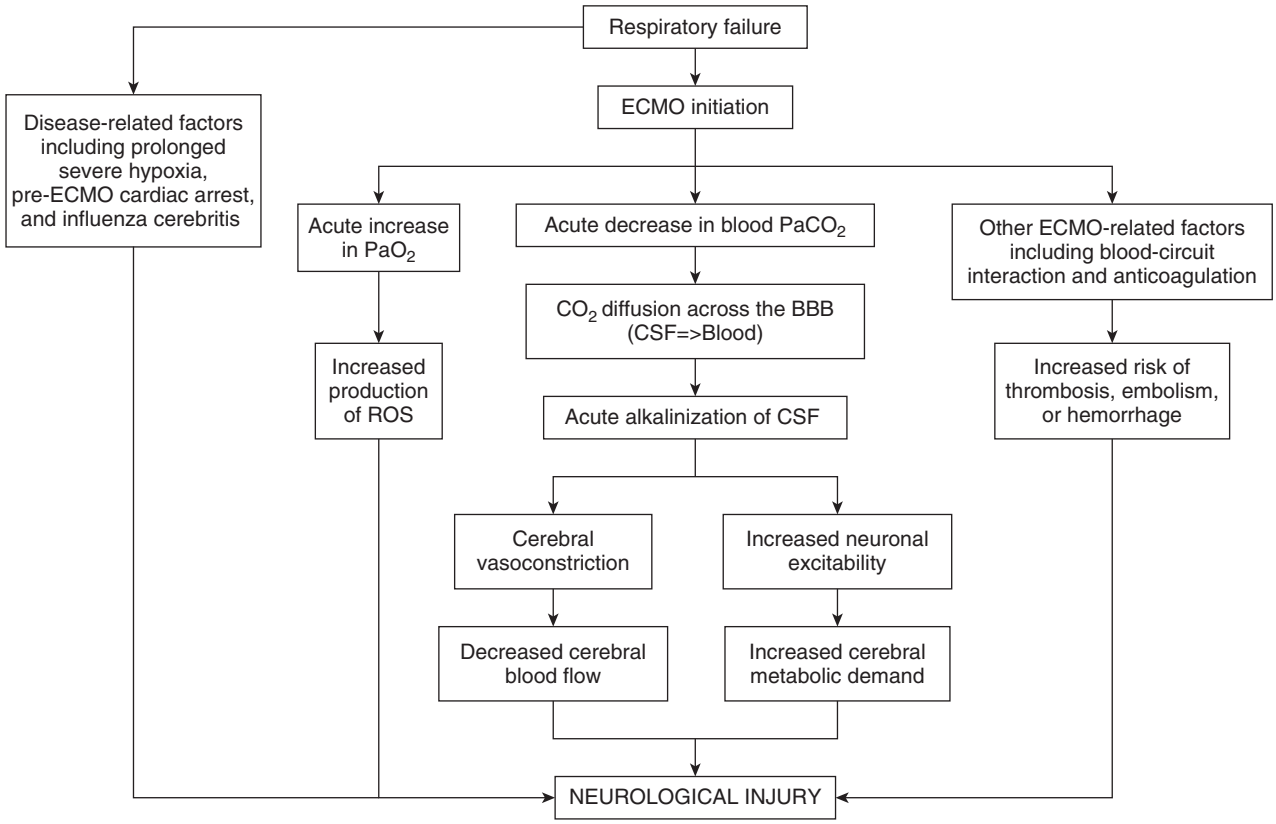

Figure 5. Pathogenesis of neurological injury occurring in patients with respiratory failure with large early changes in Pa_{CO_2} after initiation of ECMO. BBB = blood–brain barrier; CSF = cerebrospinal fluid; ECMO = extracorporeal membrane oxygenation; ROS = reactive oxygen species.

In patients receiving ECMO for respiratory failure, a high relative decrease in Pa_{CO_2} in the first 24 hours of ECMO initiation appears to be independently associated with an increased incidence of neurological complications, including seizures, stroke, intracranial hemorrhage, and brain death. This finding has important implications for the management of patients with respiratory failure being supported with ECMO. Future research should focus on determining the optimal Pa_{CO_2} correction rate in this patient population and on whether our findings also apply to patients with hypercapnic respiratory failure not receiving ECMO. Until then, our data suggest that clinicians should monitor ABGs frequently and use modest sweep gas flow rates initially to limit the magnitude of the correction in Pa_{CO_2} in the first 24 hours in patients with respiratory failure supported with ECMO. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors acknowledge the contribution of John Matelski, biostatistician at the Biostatistics Research Unit at the University Health Network (Toronto, ON, Canada), for his help with the preliminary data analysis. Moreover, the authors thank Peter Rycus (ELSO, Ann Arbor, MI) for providing the data necessary for this analysis.

References

1. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, *et al*.; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018;378:1965–1975.
2. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, *et al*. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure: the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med* 2014;189: 1374–1382.
3. Luyt C-E, Bréchot N, Demondion P, Jovanovic T, Hékimian G, Lebreton G, *et al*. Brain injury during venovenous extracorporeal membrane oxygenation. *Intensive Care Med* 2016;42:897–907.
4. Bembea MM, Lee R, Masten D, Kibler KK, Lehmann CU, Brady KM, *et al*. Magnitude of arterial carbon dioxide change at initiation of extracorporeal membrane oxygenation support is associated with survival. *J Extra Corpor Technol* 2013;45: 26–32.
5. Kredel M, Lubnow M, Westermaier T, Müller T, Philipp A, Lotz C, *et al*. Cerebral tissue oxygenation during the initiation of venovenous ECMO. *ASAIO J* 2014;60:694–700.
6. Muellenbach RM, Kilgenstein C, Kranke P, Küstermann J, Kredel M, Roewer N, *et al*. Effects of venovenous extracorporeal membrane oxygenation on cerebral oxygenation in hypercapnic ARDS. *Perfusion* 2014;29:139–141.
7. Lorusso R, Gelsomino S, Parise O, Di Mauro M, Barili F, Geskes G, *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* 2017;45:1389–1397.
8. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.
9. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
10. Nin N, Muriel A, Peñuelas O, Brochard L, Lorente JA, Ferguson ND, *et al*.; VENTILA Group. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med* 2017;43:200–208.
11. Roberts BW, Karagiannis P, Coletta M, Kilgannon JH, Chansky ME, Trzeciak S. Effects of $PaCO_2$ derangements on clinical outcomes after cerebral injury: a systematic review. *Resuscitation* 2015;91: 32–41.
12. Willie CK, Tzeng Y-C, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol* 2014;592:841–859.
13. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *J Physiol* 2011;589: 3039–3048.
14. Pollock JM, Deibler AR, Whitlow CT, Tan H, Kraft RA, Burdette JH, *et al*. Hypercapnia-induced cerebral hyperperfusion: an underrecognized clinical entity. *AJNR Am J Neuroradiol* 2009;30:378–385.
15. Roh D, Merkler AE, Al-Mufti F, Morris N, Agarwal S, Claassen J, *et al*. Global cerebral edema from hypercapnic respiratory acidosis and response to hyperosmolar therapy. *Neurology* 2016;86:1556–1558.
16. Chaudhary S, Wahab A, Varghese S, Smith SJ. Hypercapnia-induced cerebral oedema in a patient with COPD exacerbation: a rare and under-recognised entity. *BMJ Case Rep* 2017;2017:bcr2017221568.
17. Sobczyk O, Battisti-Charbonney A, Fierstra J, Mandell DM, Poublanc J, Crawley AP, *et al*. A conceptual model for CO_2-induced redistribution of cerebral blood flow with experimental confirmation using BOLD MRI. *Neuroimage* 2014;92:56–68.
18. Cold GE. Cerebral blood flow in acute head injury: the regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. *Acta Neurochir Suppl (Wien)* 1990;49:1–64.
19. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med* 2010;38:1348–1359.
20. Huttunen J, Tolvanen H, Heinonen E, Voipio J, Wikström H, Ilmoniemi RJ, *et al*. Effects of voluntary hyperventilation on cortical sensory responses: electroencephalographic and magnetoencephalographic studies. *Exp Brain Res* 1999;125:248–254.
21. Wirrell EC, Camfield PR, Gordon KE, Camfield CS, Dooley JM, Hanna BD. Will a critical level of hyperventilation-induced hypocapnia always induce an absence seizure? *Epilepsia* 1996;37:459–462.
22. Bergsholm P, Gran L, Bleie H. Seizure duration in unilateral electroconvulsive therapy: the effect of hypocapnia induced by hyperventilation and the effect of ventilation with oxygen. *Acta Psychiatr Scand* 1984;69:121–128.
23. Coles JP, Fryer TD, Coleman MR, Smielewski P, Gupta AK, Minhas PS, *et al*. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. *Crit Care Med* 2007;35: 568–578.
24. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. *Stroke* 1997; 28:1569–1573.
25. Safar P, Xiao F, Radovsky A, Tanigawa K, Ebmeyer U, Bircher N, *et al*. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. *Stroke* 1996;27:105–113.
26. Liem KD, Kollée LA, Hopman JC, De Haan AF, Oeseburg B. The influence of arterial carbon dioxide on cerebral oxygenation and haemodynamics during ECMO in normoxaemic and hypoxaemic piglets. *Acta Anaesthesiol Scand Suppl* 1995;107:157–164.
27. Gluck SL. Acid-base. *Lancet* 1998;352:474–479.
28. Ryan CM, Battisti-Charbonney A, Sobczyk O, Mikulis DJ, Duffin J, Fisher JA, *et al*. Evaluation of cerebrovascular reactivity in subjects with and without obstructive sleep apnea. *J Stroke Cerebrovasc Dis* 2018;27:162–168.
29. Le Guennec L, Cholet C, Huang F, Schmidt M, Bréchot N, Hékimian G, *et al*. Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation. *Ann Intensive Care* 2018;8: 129.
30. Cavayas YA, Del Sorbo L, Fan E. Intracranial hemorrhage in adults on ECMO. *Perfusion* 2018;33:42–50.
31. Mazzeffi M, Kon Z, Menaker J, Johnson DM, Parise O, Gelsomino S, *et al*. Large dual-lumen extracorporeal membrane oxygenation cannulas are associated with more intracranial hemorrhage. *ASAIO J* 2019;65:674–677.
32. Lockie CJA, Gillon SA, Barrett NA, Taylor D, Mazumder A, Paramesh K, *et al*. Severe respiratory failure, extracorporeal membrane oxygenation, and intracranial hemorrhage. *Crit Care Med* 2017;45: 1642–1649.
33. Sutter R, Tisljar K, Marsch S. Acute neurologic complications during extracorporeal membrane oxygenation: a systematic review. *Crit Care Med* 2018;46:1506–1513.
34. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.