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The primary objective was to investigate the association between partial pressure of carbon dioxide ($PaCO_2$) change after extracorporeal membrane oxygenation (ECMO) initiation and neurologic outcome in neonates treated for respiratory failure. A retrospective analysis of the Extracorporeal Life Support Organization (ELSO) database including newborns supported by ECMO for respiratory indication during 2015–2020. The closest Pre-ECMO (Pre-ECMO $PaCO_2$) and at 24 hours after ECMO initiation (H24 $PaCO_2$) $PaCO_2$ values allowed to calculate the relative change in $PaCO_2$ (Rel Δ $PaCO_2$ = [H24 $PaCO_2$ − Pre-ECMO $PaCO_2$]/Pre-ECMO $PaCO_2$). The primary outcome was the onset of any acute neurologic event (ANE), defined as cerebral bleeding, ischemic stroke, clinical or electrical seizure, or brain death during ECMO. We included 3,583 newborns (median age 1 day [interquartile range {IQR}, 1–3], median weight 3.2 kg [IQR, 2.8–3.6]) from 198 ELSO centers. The median Rel Δ $PaCO_2$ value was −29.9% [IQR, −46.2 to −8.5]. Six hundred nine (17%) of them had ANE (405 cerebral bleedings, 111 ischemic strokes, 225 seizures, and 6 brain deaths). Patients with a decrease of $PaCO_2$ > 50% were more likely to develop ANE than others (odds ratio [OR] 1.78, 95% confidence interval [CI], 1.31–2.42, p < 0.001). This was still observed after adjustment for all clinically relevant confounding factors (adjusted OR 1.94, 95% CI, 1.29–2.92, p = 0.001). A significant decrease in $PaCO_2$ after ECMO start is associated with ANE among neonates requiring ECMO for respiratory failure. Cautious $PaCO_2$ decrease should be considered after start of ECMO therapy. *ASAIO Journal* 2023; 69;411–416

Key Words: extracorporeal membrane oxygenation, partial pressure of carbon dioxide, acute neurologic event, neonate, respiratory failure

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The study was approved by the local Ethics Committee (date October 15, 2020).

All deidentified data were provided by the Extracorporeal Life Support Organization (www.elso.org).

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Patients requiring extracorporeal membrane oxygenation (ECMO) present a high risk of developing neurologic complications which lead to a significant morbidity and mortality, and among children, neonates represent the most vulnerable population.[1–6] The period surrounding start of ECMO is crucial as the brain is exposed to dramatic changes in cerebral oxygenation and hemodynamics. Several studies have consistently shown that most of the neurologic complications occur early during ECMO run.[7–10] The cerebral vasculature responds to carbon dioxide (CO_2) changes by a physiologic mechanism called CO_2 reactivity. A rise in partial pressure of CO_2 ($PaCO_2$) leads to cerebral vasodilation, whereas a decrease causes a vasoconstriction.[11–14] During ECMO support, the device can take up most of the native lung gas exchange, and $PaCO_2$ is tightly regulated by adjusting the fresh gas flow to the oxygen blender. Previous studies in adults have demonstrated an independent association between the magnitude of the decrease of $PaCO_2$ after ECMO initiation and neurologic outcome or mortality.[15–17] In one pediatric study including patients supported by ECMO (regardless of indications), the magnitude of $PaCO_2$ change at ECMO initiation was independently associated with mortality.[18] However, this issue has never been fully scrutinized in neonatal population.

In this context, the main objective of this study was to investigate the association between changes in $PaCO_2$ after ECMO initiation and the occurrence of neurologic complications in neonates treated for refractory respiratory failure.

Methods

Study Design and Patients

We conducted a retrospective study including newborns (≤ 28 days) supported by ECMO for respiratory indication and reported to the Extracorporeal Life Support Organization (ELSO) between January 2015 and January 2020. The current study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (http://www.strobe-statement.org/) and was approved by the Research Ethics Board of the University of Nantes, France, and the ELSO scientific oversight committee. All ECMO modes were included: venovenous (VV), venoarterial (VA), or venovenoarterial (VVA). In case of multiple ECMO runs, only the first one was considered in the analysis. In case of missing data regarding pre-ECMO or post-ECMO $PaCO_2$ values or regarding at least one variable defining acute neurologic event (ANE) as detailed below, the patient was excluded from the analyses. Furthermore, patients with pre-ECMO $PaCO_2$ > 200 mm Hg, considered as outliers, were excluded.

The ELSO provided deidentified ECMO center number, demographic, and pre-ECMO medical condition data including primary diagnosis codes according to the International Classification of Diseases (ICD), 9th Edition and ICD, 10th Edition. The presence of a congenital diaphragmatic hernia (CDH) was in addition independently reported. All diagnoses referring to a congenital heart disease were secondarily collapsed into a single item. The onset of a cardiac arrest, vital parameters, arterial blood gases (ABGs) values and ventilator settings before ECMO were also reported. Extracorporeal life support (ECLS) mode, site of cannulation, and blood pump flow at 4 and 24 hours were available. Post-ECMO ventilator settings, ABG values, and main ECLS complications according to ELSO definition were also reported.

$PaCO_2$ Values Data

The Pre-ECMO $PaCO_2$ value refers to the ABG closest to ECMO start but within 6 hours before, and the H24 $PaCO_2$ is the $PaCO_2$ value closest to 24 hours, not less than 6 hours and not more than 30 hours after ECMO initiation. The main variable of interest, considered as the exposure, was change in $PaCO_2$ expressed with absolute and relative values (Abs Δ $PaCO_2$ and Rel Δ $PaCO_2$ respectively) calculated as follows:

Abs Δ $PaCO_2$ = H24 $PaCO_2$ – Pre-ECMO $PaCO_2$ (mm Hg)

Rel Δ $PaCO_2$ = (H24 $PaCO_2$ – Pre-ECMO $PaCO_2$)/Pre-ECMO $PaCO_2$ (%)

Outcomes

The primary outcome was the occurrence of any ANE during ECMO support. Patients presenting cerebral bleeding or ischemic stroke or clinical or electrical seizure or brain death were considered ANE+.[15,19] Cerebral bleeding was defined as the onset of an intraventricular cerebral hemorrhage or intra- or extraparenchymal cerebral hemorrhage diagnosed by ultrasounds, computed tomography, or magnetic resonance imaging. The secondary outcome was 28 day mortality.

Statistical Analysis

Baseline characteristics of the patients were reported as median (interquartile range [IQR]) or mean (standard deviation) for quantitative variables and and n (%) for qualitative variables, respectively. Abs Δ $PaCO_2$ and Rel Δ $PaCO_2$ were transformed into categorical variables. For descriptive analysis, Abs Δ $PaCO_2$ and Rel Δ $PaCO_2$ were first expressed with a large panel of bins of 20 mm Hg and 20%, respectively. The extreme bins were secondarily grouped to obtain representative group sizes. The comparison of the characteristics of ANE– and ANE+ patients was performed using the χ^2 test for nominal variables and the Mann–Whitney *U* test for continuous variables.

First, for our primary analysis, multivariable logistic regression was performed to assess the association between Rel Δ $PaCO_2$ and ANE using generalized estimating equation (GEE) model taking into account the identification of the ECMO center to reduce the bias because of local practices. Variables representing an event that potentially occurred after H24 of ECMO were not considered. The following clinically relevant variables were included in the model: the volume of ECMO of the centers (represented by the number of patients from each center in the overall study database), characteristics of the newborns (sex, prematurity [gestational age < 37 weeks], Apgar score at 5 minutes of life, age and weight at cannulation, CDH, meconium aspiration syndrome [MAS], and congenital heart disease), pre-ECMO medical condition (cardiac arrest before ECMO start, ventilation type, mean blood pressure, oxygenation index, bicarbonates, ECMO mode), post-ECLS variables (ventilation type after 24 hours of ECMO, pump flow 4 and 24 hours after ECMO start), and Rel Δ $PaCO_2$. All variables were assessed for multicollinearity using tolerance statistics (values of variance inflation factor > 2 indicative of multicollinearity), and in such cases, only one member of a correlated set was retained for the final model. Results were summarized using odds ratios (ORs) and 95% confidence intervals (CIs). The goodness of fit for GEE was assessed by the *C*-statistic.

Second, we performed several sensitivity analyses using GEE. We investigated the association between Rel Δ $PaCO_2$ and ANE according to Pre-ECMO after dividing the cohort into quartiles. We also assessed the association between Abs Δ $PaCO_2$ (instead of Rel Δ $PaCO_2$) and ANE and between Rel Δ $PaCO_2$ and the composite outcome "ANE or death by any cause" to account for competing risk which is death. Subgroups analyses focusing on patients treated for CDH and for MAS respectively and supported by VA or VVA and VV ECMO respectively were also performed. For all these analyses, the same variables were included in the GEE models as for the primary one.

Third, we investigated the crude and adjusted association between Rel Δ $PaCO_2$ and 28 day mortality performing survival analysis by Cox regression model of time-to-death. The same variables as in the primary analysis were included in the model. The proportional-hazards assumption was assessed using Schoenfeld residuals-based test.

Missing values were not imputed. In all analyses, *p* value of less than 0.05 was considered as significant. Statistical analysis was performed using SPSS 19 software (IBM Corp., Chicago, IL).

Results

Study Population

Four thousand seventy-two newborns from 198 centers supported by ECMO for respiratory indication were reported to the ELSO during the study period, and 3,583 of them were included in the analysis (Figure 1). The most frequently reported

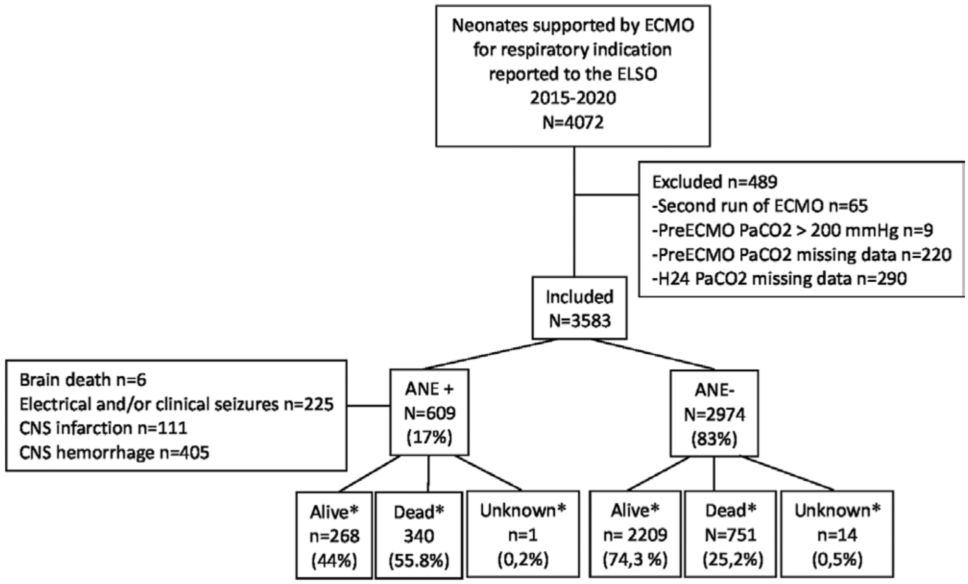

Figure 1. Flowchart of the study population. Pre-ECMO partial pressure of carbon dioxide ($PaCO_2$): closest to and before ECMO start values, within 6 hours before ECMO start. H24 $PaCO_2$: closest to 24 hours after ECMO start values, not less than 6 hours and not more than 30 hours after ECMO start. *At hospital discharge. CNS, central nervous system; ECMO, extracorporeal membrane oxygenation.

primary diagnoses were CDH (n = 1,247; 34.8%), MAS (n = 740; 20.7%), pulmonary hypertension (n = 472; 13.2%), and infectious diseases (n = 172; 4.8%). A congenital heart disease was reported as primary diagnosis in 45 (1.3%) patients. Baseline characteristics of the whole population are described in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883).

Outcomes

The median duration of ECMO among the whole population was 6.6 days (IQR, 4.2–11.8). As shown in Figure 1, 609 (17%) newborns met at least one criterion defining ANE, mostly represented by CNS hemorrhage (n = 405, 11.3% of the newborns). Baseline characteristics according to neurologic status are presented in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883). The overall 28 day mortality in the whole population was 20.8% and was higher among ANE+ as compared with ANE− patients (45.3 *vs*. 15.7%, $p < 0.001$).

Distribution of $PaCO_2$ Variations

The mean H24 $PaCO_2$ value was significantly lower as compared with pre-ECMO $PaCO_2$ value (43.3 ± 10 *vs*. 65.5 ± 25.1, $p < 0.001$), and the median absolute and relative changes of $PaCO_2$ were −18 mm Hg (−35 to −4) and −29.9% (−46.2 to −8.5), respectively. Supplementary Figure 1 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A884) shows the distribution of Abs Δ $PaCO_2$ and Rel Δ $PaCO_2$ values, and the characteristics of the patients according to Rel Δ $PaCO_2$ group are presented in Supplementary Table 2 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883).

Relative $PaCO_2$ Variations and Neurologic Outcome

The relative change of $PaCO_2$ was significantly lower (more negative) among ANE+ patients compared with others (median values [IQR] −33.6% [−50.6 to −12.3] *vs*. −17.5% [−34 to −3.8], $p = 0.001$). Supplementary Table 3 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883) shows the unadjusted risk of ANE according to the relative change of $PaCO_2$. Considering Rel Δ $PaCO_2$ values between −10% and +10% as the reference, a decrease of $PaCO_2$ > 50% was significantly associated with ANE (OR 1.78, 95% CI, 1.31–2.42, $p < 0.001$). No variables were omitted for collinearity. After adjustment for all clinically relevant variables, a decrease of $PaCO_2$ > 50% remained significantly associated with ANE (adjusted OR [aOR] 1.94, 95% CI, 1.29–2.92, $p = 0.001$). Supplementary Table 4 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883) shows the same trends whatever the baseline value of $PaCO_2$, even all classes of Rel Δ $PaCO_2$ could not be analyzed for each quartile of Pre-ECMO $PaCO_2$. As presented in Supplementary Table 5 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883), similar results were found considering absolute values of $PaCO_2$ variations instead of relatives ones as a decrease of $PaCO_2$ > 50 mm Hg was also significantly associated with ANE (aOR 1.56, 95% CI, 1.11–2.17, $p = 0.009$). As shown in Supplementary Table 6 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A883), all bins of Rel Δ $PaCO_2$ representing a decrease or an increase of $PaCO_2$ were independently associated with an increased risk of ANE or death. Finally, Figure 2 illustrates the association between a decrease of $PaCO_2$ > 50% and ANE within the subgroups of patients supported by VA or VVA ECMO and VV ECMO respectively and those treated for CDH and MAS respectively.

$PaCO_2$ Change and Mortality

In univariate analysis, Rel Δ $PaCO_2$ was associated with increased 28 day mortality after ECMO start for all bins as compared with the reference (−10% to 10%). The crude hazard ratios for the risk of 28 day mortality were 2.14 (95% CI, 1.63–2.81, $p < 0.001$) for a decrease of $PaCO_2$ > 50%, 1.52 (95% CI, 1.16–1.99, $p = 0.002$) between 30% and 50%, 1.52

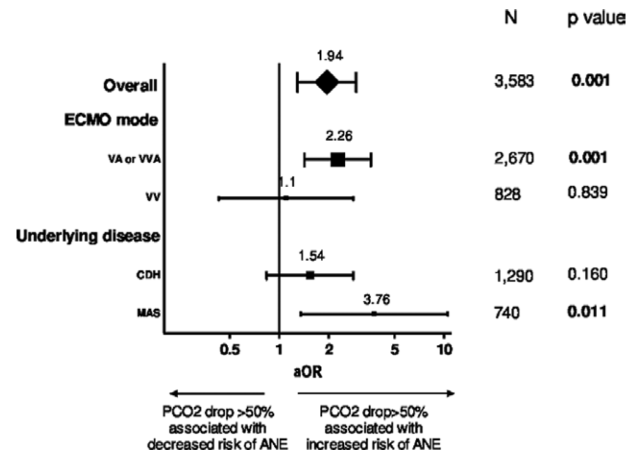

Figure 2. Subgroup analysis of the association of a partial pressure of carbon dioxide ($PaCO_2$) drop > 50% with the risk of ANE. Comparison was made with Rel $\Delta PaCO_2$ between −10% and 10%. Multivariate analysis was performed using generalized estimating equation model taking into account the identification of the ECMO center. Results are expressed as aOR (95% CI). p value < 0.05 was considered as significant (in bold). ANE, acute neurologic event; aOR, adjusted odds ratio; CI, confidence interval; ECMO, extra corporeal membrane oxygenation; CDH, congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; VA, venoarterial; VV, venovenous; VVA, venovenoarterial; Rel $\Delta PaCO_2$, relative change in $PaCO_2$ = (H24 $PaCO_2$ −Pre-ECMO $PaCO_2$)/Pre-ECMO $PaCO_2$.

(95% CI, 1.15–2, $p = 0.003$) between 10% and 30%, and 1.82 (95% CI, 1.34–2.47, $p < 0.001$) an increase of $PaCO_2$ > 10%.

As shown in Supplementary Figure 2 (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A884), the time-to-death multivariate survival analysis according to relative change in $PaCO_2$ demonstrated increased 28 day mortality for all bins of Rel Δ $PaCO_2$ representing a decrease or an increase of $PaCO_2$ as compared to a low $PaCO_2$ change.

Discussion

The presented 5 year analysis of the worldwide ELSO database includes 3,583 newborns requiring ECMO for respiratory failure in 198 centers. We reported an independent association between a severe decrease (more than 50%) of $PaCO_2$ after ECMO start and the occurrence of ANE during ECMO support. Second, we found an association between the relative $PaCO_2$ change and 28 day mortality. As Δ $PaCO_2$ is partially controllable (contrary to other variables included in our analyses), these results appear of major interest. Indeed, they suggest that $PaCO_2$ should be closely monitored and that the magnitude of $PaCO_2$ decreases after ECMO start should be limited, in particular for preterms and patients who require ECMO after cardiac arrest.

These results confirm previous studies among adults supported by ECMO for respiratory indication and in the context of hemodynamic failure.[15–17] Only one pediatric study had investigated this issue before.[18] In this single-center study including 201 children supported by VA or VV ECMO for all indications, Bembea *et al.*[18] demonstrated that the magnitude of $PaCO_2$ decrease (≥ 25 mm Hg) was independently associated with mortality. However, this study did not investigate the impact of $PaCO_2$ change on neurologic outcome. In our study, the impact of the relative Δ $PaCO_2$ on the risk of ANE was only statistically significant when the magnitude was ≥ 50% (and also was ≥ 50 mm Hg) which may appear extreme. However, this situation is not uncommon as, in our population, 717 (20%) newborns were exposed to such variations. In the previously cited adult study from Cavayas *et al.*,[15] including 11,972 patients under VV ECMO for respiratory failure, the median relative change in $PaCO_2$ was −31%, very close to our results, and a relative $PaCO_2$ decrease ≥ 50% was also independently associated with an increased risk of ANE. In the publication from Diehl *et al.*[16] including adult patients supported by VA ECMO for hemodynamic failure, the mean pre-ECMO $PaCO_2$ was 45.5 mm Hg, very different from our results (median value 60 mm Hg) and from the study by Cavayas *et al.*[15] (median value 59 mm Hg). They also found an association between $PaCO_2$ change and poor outcome from a decrease of more than 7.5 mm Hg in $PaCO_2$, suggesting that even small $PaCO_2$ decrease can be harmful in the absence of severe hypercapnia before ECMO.

In other critical conditions, mild hypercapnia has been proposed as a potential treatment target to improve outcomes.[20] It is well established that decrease in $PaCO_2$ causes dose-dependent vasoconstriction leading to the risk of cerebral ischemia.[14,21] Furthermore, it is known from animal models that hypercapnia attenuates hypoxic-ischemic brain injury in the immature rat and protects the porcine brain from reoxygenation injury by attenuation of free radical action.[22,23]

Otherwise, cerebral autoregulation (CA) impairment is frequently observed under ECMO and may take part in the genesis of neurologic complications.[10,24,25] The direct consequence of the nonpulsatile blood flow provided by ECMO has been suggested by experimental studies as a potential underlying mechanism.[26–29] The impact of $PaCO_2$ value and $PaCO_2$ variations on CA in this context remains unclear, but some experimental studies have suggested a protective effect of hypercapnia regarding CA.[11,30] In a recent study including 30 children supported by ECMO for all indications, we have shown that the level of $PaCO_2$ was positively correlated with the upper limit of CA, supporting that hypothesis of a protective effect of hypercapnia on CA, in case of high blood pressure and nonpulsatile flow.[31] However, this study did not investigate the relationship between $PaCO_2$ changes and CA. Nevertheless, as children supported by ECMO are frequently exposed to dramatic blood pressure increase and $PaCO_2$ variations at the same time after its onset, this result appears clinically relevant.[8,18,32] This may be a plausible explanation for the independent association between $PaCO_2$ decrease after ECMO start and the risk of cerebral bleeding found in adult studies.[15,17] Even though this association was not significant in our study, we observed the same trend.

Otherwise, it has been demonstrated that hypocapnia increases neuronal excitability, resulting in increased oxygen consumption and uncoupling of metabolism to cerebral blood flow and may be directly neurotoxic.[33,34] In a pediatric study including 484 patients supported by ECMO for all indications, hypocapnia defined by a $PaCO_2$ < 30 Torr was encountered in 20.2% of children within the first 48 hours of ECMO, and these patients had more neurologic events.[35]

Unlike in adult studies, we found an increased risk of 28 day mortality in case of $PaCO_2$ increase (> 10%) which appears discordant with the potential protective effect of hypercarbia previously mentioned and remains difficult to interpret. As compared with patients with a minimal $PaCO_2$ change, those presenting an increase of $PaCO_2$ > 10% presented no differences regarding baseline characteristics. One could imagine that an increase of $PaCO_2$ could be the consequence of technical difficulties, but the lack of difference with regard with ECMO flow 4 and 24 hours after ECMO initiation was not in favor of this hypothesis.

Limitations

Our study presents some important limitations. First, the number of data collected by the ELSO registry remains limited, and residual confounders could not be included in the analysis. In particular, the first provided H24 $PaCO_2$ included values between 6 and 30 hours after ECMO start which is probably not strictly representative of acute change of $PaCO_2$ at the time of ECMO initiation. An earlier $PaCO_2$ value as used by Bembea *et al.*[18] or repeated values during this initial period would be of major interest to study more specifically the relationship between $PaCO_2$ changes and neurologic outcome. Furthermore, the onset of any ANE before ECMO initiation was not reported in the database, and some pathologic triggers potentially affecting neurologic outcome may have occurred within the first 24 hours of ECMO and were not taken into account in the analysis.

Second, in our analyses, $PaCO_2$ changes were treated using categorical variables which can be discussed. This methodological choice was based on the opposite physiologic effects of the decrease and the increase in $PaCO_2$ on cerebral vasculature, making expecting a U-shape relationship between the change in $PaCO_2$ and neurologic outcome. As presented in Supplementary Table 3 (Supplemental Digital Content, http://links.lww.com/ASAIO/A883), our results have shown a trend for an increased risk of ANE in case of increase in $PaCO_2$ (> 10%) that may confirm this hypothesis.

Third, when interpreting our results, it must be noted that the effect of the CO_2 decrease on outcomes is inevitably confounded by the baseline $PaCO_2$ which in itself is representative of the severity of the illness. In this context, information regarding the sweep gas flow but also minute ventilation in the mechanical ventilator may be of major interest for the interpretation of the impact of the settings made by the clinicians on changes of $PaCO_2$ and on outcomes. Even if our statistical analysis aimed to reduce this bias taking into account many variables representative of the severity of the illness, this point remains questionable, and only randomized study comparing different strategies for controlling $PaCO_2$ after ECMO start would allow to fully answer the question.

Fourth, as the timing of the onset of neurologic complications from the ECMO initiation was unknown, we could not perform any time-dependent analysis of the association between $PaCO_2$ changes and the risk of ANE which represents a limitation for the interpretation of the results.

Last, the analysis of mortality was limited by the lack of available data representing illness severity such as pre-ECMO renal or liver failure, or some measure of risk of mortality.

Conclusions

Among newborns requiring ECMO for respiratory failure, this study has demonstrated an independent association between a significant decrease of $PaCO_2$ after ECMO start and the risk of developing ANE during ECMO run. Even though no causal effect can be extrapolated from these results, they suggest a need of very close monitoring and cautious settings of the fresh gas flow to limit the magnitude of $PaCO_2$ decrease during this critical period. Further studies are needed to establish the optimal rate of change of $PaCO_2$ after ECMO initiation.

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