

ORIGINAL RESEARCH

Carbon Dioxide Levels in Extremely Preterm Neonates Ventilated With High Frequency Jet Ventilation

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Abstract

Background: Close monitoring of carbon dioxide (CO₂) levels is crucial in extremely preterm neonates; however, a consensus on the optimal CO₂ thresholds is lacking. We aimed to evaluate the impact of P_aCO₂ levels during the first 24 h of life on the outcomes of extremely preterm neonates ventilated with first-intention high frequency jet ventilation (HFJV).

Methods: We retrospectively examined neonates ≤26 weeks of gestational age who were ventilated with first-intention HFJV, during 2022–2024, comparing the lowest P_aCO₂, peak P_aCO₂, P_aCO₂ fluctuations, and P_aCO₂ deviation from the target (40–50 mm Hg) during the first 24 h of life between neonates who survived without severe intraventricular hemorrhage (IVH) and neonates who developed severe IVH or died.

Results: Among 50 extremely preterm neonates of gestational age 24.3 ± 1.5 weeks and birthweight 656 ± 170 g, 33 (66%) survived without severe IVH. Neonates who survived without severe IVH were of greater gestational age (24.7 ± 1.3 vs 23.6 ± 1.5 weeks, *P* = .01) and birthweight (696 ± 159 vs 577 ± 167 g, *P* = .02), compared to neonates who developed severe IVH or died. The latter had significantly higher peak P_aCO₂ (66.7 ± 17.0 vs 54.6 ± 10.2 mm Hg, *P* = .006), P_aCO₂ fluctuations (30.8 ± 17.3 vs 16.6 ± 8.8 mm Hg, *P* = .001), and P_aCO₂ deviation from the target (20.0 ± 14.9 vs 9.7 ± 7.3 mm Hg, *P* = .003), compared to neonates who survived without severe IVH. A higher peak P_aCO₂, P_aCO₂ fluctuation, and P_aCO₂ deviation from the target were significantly associated with severe IVH, death, or severe IVH/death. A cutoff of a peak P_aCO₂ <65 mm Hg, P_aCO₂ fluctuation <25 mm Hg, and P_aCO₂ deviation <15 mm Hg from the target had the best sensitivity and specificity for survival, absence of severe IVH, and survival without severe IVH.

Conclusions: In extremely preterm neonates ventilated with first-intention HFJV, maintaining peak P_aCO₂ of <65 mm Hg, P_aCO₂ fluctuations <25 mm Hg, and P_aCO₂ deviation from target <15 mm Hg was significantly associated with survival without severe IVH.

Keywords: carbon dioxide, high-frequency jet ventilation, intraventricular hemorrhage, intracranial pathology, preterm

Introduction

In preterm newborns, an association between CO₂ levels and brain abnormalities has previously been suggested.^{1,2} It has been proposed that both hyper- and hypocapnia may be harmful to newborns because of the physiological effects of CO₂ levels on the cerebral vasculature and immunological signaling. In hypoxic

situations, several adaptive cerebral vasodilatory processes are activated to enhance and maintain cerebral blood flow. Elevated CO₂ increases cerebral blood flow by promoting cerebral arterial dilation, whereas hypocapnia results in vascular constriction and decreased blood flow.³ However, preterm neonates are unable to maintain the balance of cerebral vascular circulation, as

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these infants have insufficient vascular bed reactivity to blood CO₂ levels.⁴

Prior studies have shown that hypocapnia is associated with periventricular leukomalacia, underscoring the need for close monitoring of blood CO₂ levels in preterm newborns.^{5,6} However, it is unclear whether hypocapnia is the cause or consequence of cerebral injury leading to periventricular leukomalacia.^{7,8} On the contrary, neonates receiving high frequency jet ventilation (HFJV) often have low P_{aCO₂} levels without developing periventricular leukomalacia.^{9,10} The connection between intraventricular hemorrhage (IVH) and CO₂ variations has also been highlighted in prior studies.¹¹ Some studies suggest that acidosis is a more reliable indicator of cranial bleeding than partial pressure of CO₂, whereas others suggested that this association is more closely linked to CO₂ variations than CO₂ levels.^{12,13}

There is currently a lack of consensus about optimal CO₂ values for these vulnerable newborns and very little data on best clinical practices for treating newborns with moderate hypercapnia and hypocapnia. Although there is agreement that a protocolized initial ventilatory approach improves outcomes for extremely preterm neonates,¹⁴ there is disagreement among experts regarding the best initial, or first-intention, ventilatory strategy,^{14–16} with some studies supporting the use of first-intention HFJV.¹⁷ One benefit of HFJV is that it uses high breathing frequencies to produce minute ventilation with tidal volumes less than physiologic dead space, thereby decreasing the risk of barotrauma and volutrauma because of the decreased supplied pressure to the alveoli.^{16,18} In this study, we aimed to examine the impact of P_{aCO₂} levels during the first 24 h of life on outcomes of extremely preterm neonates who were ventilated with first-intention HFJV.

Methods

We conducted a retrospective cohort study including all extremely preterm neonates of ≤26 weeks of gestational age who were ventilated with first-intention HFJV in our level III neonatal ICU, at Brigham and Women's Hospital, Boston, MA, United States, between October 2022 and June 2024. The study was approved by the institutional review board (Protocol Number 2023P001168/05.05.2023).

In our institution, HFJV has been established as the initial ventilation strategy within the Small Baby Program. The launch of the Small Baby Program emphasized the need for a standardized ventilator approach for these vulnerable infants, with HFJV as the preferred initial ventilator mode based on our acquired experience with HFJV, recognition of the theoretical advantages of HFJV, evidence from published studies, and discussions of institutional experience in other small baby programs,

QUICK LOOK

Current knowledge

In preterm neonates, both hyper- and hypocapnia may be harmful, as an association between CO₂ levels and brain abnormalities has been suggested. However, a consensus on the optimal CO₂ thresholds is lacking.

What this paper contributes to our knowledge

In extremely preterm neonates receiving first-intention high frequency jet ventilation, peak P_{aCO₂} of <65 mm Hg, P_{aCO₂} fluctuations of <25 mm Hg, and P_{aCO₂} deviation from the target of <15 mm Hg were significantly associated with survival, absence of severe intraventricular hemorrhage (IVH), and survival without severe IVH.

such as the program at the University of Iowa.^{14,18} The initial settings on first-intention HFJV mode [Model 203 Life Pulse High-Frequency Ventilator (Jet), Bunnell, Inc., Salt Lake City, UT, United States] were: frequency: 300–360 breaths/min, inspiratory time: 0.02 s, peak inspiratory pressure: 20–24 cm H₂O, peak end-expiratory pressure: 5–6 cm H₂O, with no backup rate. The target range for P_{aCO₂} is 40–50 mm Hg in our small baby protocol.

We collected perinatal characteristics, including gestational age, birthweight, sex, maternal complications (ie, short cervix, placenta abruption, nonreassuring fetal heart tracing, cord prolapse, preeclampsia), intrauterine growth restriction, group B *Streptococcus* colonization, prolonged rupture of membranes, chorioamnionitis, complete course of antenatal steroids, delivery mode, need for resuscitation in the delivery room, Apgar score, time of intubation, time of surfactant administration, the initial settings of HFJV, and the pH, P_{aO₂}, and P_{aCO₂} and HCO₃ values during the first 24 h of life measured by arterial blood gas analysis. Oxygenation index (OI) was calculated based on the formula: (F_{IO₂} × Mean airway pressure)/P_{aO₂}. We also recorded the duration of HFJV, the mode of ventilation before extubation, and common neonatal morbidities including pneumothorax, pulmonary hemorrhage, the need for inotropes administration, early and late-onset sepsis, necrotizing enterocolitis based on Vermont–Oxford Network criteria,¹⁹ seizures, retinopathy of prematurity, IVH, periventricular leukomalacia (diagnosed via magnetic resonance imaging at term equivalent age), the duration of invasive and noninvasive mechanical ventilation, the ventilation-free days, rates of bronchopulmonary dysplasia and grade based on Jensen definition,²⁰ postmenstrual age and birthweight on discharge, and survival. All patients' outcomes were tracked to hospital discharge regardless of transfer.

We examined the neonatal and ventilation characteristics, including the time of the first dose of surfactant administration, and the P_{aCO_2} parameters, including the mean values of the lowest P_{aCO_2} , peak P_{aCO_2} , P_{aCO_2} fluctuations (peak minus lowest value), and P_{aCO_2} deviation from target (40–50 mm Hg) during the first 24 h of life between neonates who survived without severe (grade III or intraparenchymal hemorrhage) IVH and neonates who developed severe IVH or died.

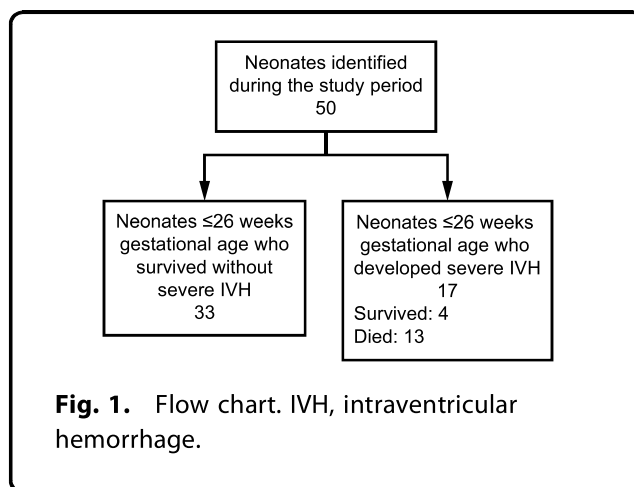
Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range), and categorical variables were expressed as n (%). The normality of the distributions of continuous variables was assessed by the Kolmogorov–Smirnov or the Shapiro–Wilk test. Comparisons between continuous variables were performed with the Student t test or the nonparametric Mann–Whitney test, as appropriate, whereas comparisons between categorical variables utilized the chi-square test or the Fisher exact test.

A multivariable logistic regression analysis was performed to examine the impact of P_{aCO_2} parameters, namely the peak P_{aCO_2} , P_{aCO_2} fluctuation, and P_{aCO_2} deviation from target, on the absence of severe IVH, survival, and survival without severe IVH, adjusted for gestational age. Given the limited number of outcome events, we have revised the analysis to minimize overfitting by restricting the number of covariates to two. Odds ratios (ORs) and 95% confidence intervals were calculated. Area under the receiver operating characteristic curve analysis was performed to detect the cutoff value of the same P_{aCO_2} parameters with the best sensitivity and specificity for the absence of severe IVH, survival, and survival without severe IVH. All performed tests were 2-sided, and a P value <0.05 was considered statistically significant ($\alpha = 0.05$). The data were analyzed using SPSS Statistics Version 25.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, United States).

Results

During the study period, we identified 50 extremely preterm neonates <26 weeks who were ventilated with first-intention HFJV. Among the 50 neonates of our cohort, 33 (66%) survived without severe IVH, whereas 17 developed severe IVH or died (Fig. 1). The perinatal characteristics of the study cohort are presented in Table 1. The mean gestational age in our cohort was 24.3 ± 1.5 weeks and birthweight 656 ± 170 g. All neonates were resuscitated in the delivery room with inflation breaths and nasal CPAP via Neopuff. In neonates of our cohort, a radiograph was routinely performed prior to surfactant administration; surfactant was administered via endotracheal tube



at a median of 39 (32–48) min of life. The frequency of the blood gases varied in our cohort between 3 and 8 gases/24 h. transcutaneous CO₂ were not often used under 22 weeks because of skin integrity. During the first 24 h of life, the mean lowest P_{aCO_2} was 37.3 ± 9.1 mm Hg, peak P_{aCO_2} was 58.6 ± 13.9 mm Hg, P_{aCO_2} fluctuation was 21.1 ± 13.8 mm Hg, and P_{aCO_2} deviation from target was 13.7 ± 10.2 mm Hg. Inotropes were administered in 29 (58%) neonates (Table 2). Among survivors, 26 (70%) neonates developed bronchopulmonary dysplasia; 4 (10%) neonates developed severe IVH at a median of 3 (1–3) days (Table 3).

The neonates who survived without severe IVH were of greater gestational age (24.7 ± 1.3 vs 23.6 ± 1.5 weeks, $P = .01$) and birthweight (696 ± 159 vs 577 ± 167 g, $P = .02$), received surfactant earlier [median 36 (31–43) vs 45 (36–53) min, $P = .01$], and required inotropes in lower rates (42% vs 88%, $P = .002$) compared to neonates who developed severe IVH or died. Moreover, neonates who survived without severe IVH were initially set on lower PEEP [5 (5–6) vs 6 (5–6) cm H₂O, $P = .02$] and higher frequency [360 (300–360) vs 300 (300–360) breaths/min, $P = .02$]. Nevertheless, neonates who developed severe IVH or died had an initial OI of 4.8 compared to 4.1 ($P = .12$) of neonates who survived without severe IVH. Neonates who developed severe IVH or died had significantly higher peak P_{aCO_2} (66.7 ± 17.0 vs 54.6 ± 10.2 mm Hg, $P = .006$), P_{aCO_2} fluctuations (30.8 ± 17.3 vs 16.6 ± 8.8 mm Hg, $P = .001$), and P_{aCO_2} deviation from the target (20.0 ± 14.9 vs 9.7 ± 7.3 mm Hg, $P = .003$), compared to neonates who survived without severe IVH (Tables 1 and 2).

In regression analysis, the level of the peak P_{aCO_2} (OR: 0.94, 95% CI: 0.88, 0.99, $P = .048$), the P_{aCO_2} fluctuation (OR: 0.93, 95% CI: 0.88, 0.99, $P = .049$), and the P_{aCO_2} deviation from the target (OR: 0.92, 95% CI: 0.84, 0.98, $P = .045$) were significantly independently associated

Table 1. Perinatal characteristics of the study population, between neonates who survived without severe intraventricular hemorrhage and neonates who developed severe intraventricular hemorrhage or died

	Total cohort (N = 50)	Survival without severe IVH (n = 33)	Severe IVH/death (n = 17)	P
Gestational age, weeks	24.3 ± 1.5	24.7 ± 1.3	23.6 ± 1.5	.01
Birthweight, g	656 ± 170	696 ± 159	577 ± 167	.02
Sex, male	31 (62%)	21 (64%)	10 (59%)	.76
Short cervix	3 (6%)	1 (3%)	2 (12%)	.26
Placenta abruption	10 (20%)	8 (24%)	2 (12%)	.46
Nonreassuring fetal heart trace	19 (38%)	12 (36%)	7 (41%)	.76
Cord prolapse	4 (8%)	2 (6%)	2 (12%)	.59
Preeclampsia	4 (8%)	1 (3%)	3 (17%)	.10
Intrauterine growth restriction	4 (8%)	3 (9%)	1 (6%)	>.99
Group B <i>Streptococcus</i> colonization	9 (18%)	7 (21%)	2 (12%)	.40
Prolonged rupture of membranes	27 (54%)	18 (55%)	9 (53%)	>.99
Chorioamnionitis	14 (28%)	10 (30%)	4 (24%)	.74
Antenatal steroids	30 (60%)	13 (39%)	7 (41%)	.99
Delivery mode, cesarean section	37 (74%)	24 (73%)	13 (77%)	.99
Delivery room resuscitation, chest compressions	5 (10%)	4 (12%)	1 (6%)	.65
Apgar 1	3 (2–5)	3 (2–6)	3 (2–4)	.49
Apgar 5	5 (3–8)	5 (4–8)	6 (3–6)	.63
Apgar 10	7 (6–9)	6 (6–9)	7 (5–8)	.91

Continuous variables are expressed as mean ± SD or median (interquartile range). *P* values of Student *t* test or Mann–Whitney test. Categorical variables are expressed as *n* (%). *P* values of chi-square test or Fisher exact test.

^aData among survivors.

IVH, intraventricular hemorrhage.

with the absence of severe IVH, after adjusting for gestational age (Table 4). Also, the level of the peak P_{aCO_2} (OR: 0.93, 95% CI: 0.88, 0.98, *P* = .02), the P_{aCO_2} fluctuation (OR: 0.91, 95% CI: 0.86, 0.97, *P* = .008), and the P_{aCO_2} deviation from the target (OR: 0.90, 95% CI: 0.84, 0.98, *P* = .01) were significantly independently associated with survival, after adjusting for gestational age

(Table 4). Finally, the level of the peak P_{aCO_2} (OR: 0.92, 95% CI: 0.88, 0.98, *P* = .008), the P_{aCO_2} fluctuation (OR: 0.91, 95% CI: 0.85, 0.97, *P* = .007), and the P_{aCO_2} deviation from the target (OR: 0.90, 95% CI: 0.83, 0.97, *P* = .01) were significantly independently associated with survival without severe IVH, after adjusting for gestational age (Table 4).

Table 2. Respiratory characteristics of the study population, between neonates who survived without severe intraventricular hemorrhage and neonates who developed severe intraventricular hemorrhage or died

	Total cohort (N = 50)	Survival without severe IVH (n = 33)	Severe IVH/death (n = 17)	P
Time of intubation, min	5 (3–8)	5 (3–9)	5 (4–8)	.76
Time of surfactant administration, min	39 (32–48)	36 (31–43)	45 (36–53)	.01
HFJV initial settings				
PIP, cm H ₂ O	22 (21–24)	22 (21–23)	24 (21–24)	.25
PEEP, cm H ₂ O	5.5 (5–6)	5 (5–6)	6 (5–6)	.02
Frequency, breaths/min	360 (300–360)	360 (300–360)	300 (300–360)	.02
Initial MAP, cm H ₂ O	8.1 ± 1.2	7.8 ± 0.8	8.6 ± 1.7	.13
Initial F _{IO₂}	0.46 (0.35–0.72)	0.45 (0.35–0.60)	0.60 (0.38–1)	.14
Initial oxygenation index	4.5 (3.4–6.5)	4.1 (3.1–5.4)	4.8 (4.4–11.5)	.12
Initial pH	7.27 ± 0.13	7.28 ± 0.0.13	7.24 ± 0.11	.34
Initial P_{CO_2} , mm Hg	47.9 ± 15.4	47.0 ± 15.8	49.9 ± 14.7	.56
Initial P_{O_2} , mm Hg	78 (56–117)	86 (59–117)	60 (54–80)	.26
Initial HCO ₃ , mmol/L	22.2 ± 4.6	22.3 ± 4.7	22.0 ± 4.7	.81
Lowest CO ₂ , mm Hg	37.3 ± 9.1	38.0 ± 9.2	35.8 ± 9.3	.48
Peak CO ₂ , mm Hg	58.6 ± 13.9	54.6 ± 10.2	66.7 ± 17.0	.006
CO ₂ fluctuation, mm Hg	21.2 ± 13.8	16.6 ± 8.8	30.8 ± 17.3	.001
CO ₂ deviation from target, mm Hg	13.7 ± 10.2	9.7 ± 7.3	20.0 ± 14.9	.003
PMA on extubation, weeks	30.3 ± 3.9	30.4 ± 4.0	29.5 ± 3.4	.58
Time on HFJV, days	2.1 (1.1–5.0)	2.1 (0.7–5.7)	2.4 (1.6–4.0)	.87
Time to extubation, weeks	4 (2–9)	4 (3–9)	5 (4–8)	.76
Mode before extubation ^a				<.001
HFJV	8 (16%)	8 (24%)	—	
Conventional	30 (60%)	25 (76%)	5 (29%)	

Continuous variables are expressed as mean ± SD or median (interquartile range). *P* values of Student *t* test or Mann–Whitney test. Categorical variables are expressed as *n* (%). *P* values of chi-square test or Fisher exact test.

^aData among survivors.

IVH, intraventricular hemorrhage; HFJV, high frequency jet ventilation; PIP, positive inspiratory pressure; MAP, mean airway pressure; PMA, postmenstrual age.

Table 3. Outcomes of the study population, between neonates who survived without severe intraventricular hemorrhage and neonates who developed severe intraventricular hemorrhage or died

	Total cohort (N = 50)	Survival without severe IVH (n = 33)	Severe IVH/death (n = 17)	P
Pneumothorax	3 (6%)	3 (10%)	—	.54
Pulmonary hemorrhage	2 (4%)	1 (3%)	1 (6%)	.99
Inotropes	29 (58%)	14 (42%)	15 (88%)	.002
Early-onset sepsis	2 (4%)	2 (6%)	—	.54
Late-onset sepsis	9 (18%)	5 (15%)	4 (24%)	.46
Necrotizing enterocolitis	7 (14%)	3 (10%)	4 (31%)	.17
Seizures	2 (4%)	—	2 (12%)	.11
Retinopathy of prematurity	21 (42%)	17 (74%)	4 (57%)	.64
Periventricular leukomalacia	1 (2%)	1 (3%)	—	.99
Invasive mechanical ventilation, days	28 (8–68)	40 (22–79)	22 (8–28)	.09
Noninvasive mechanical ventilation, days	32 (22–47)	29 (19–48)	32 (29–34)	.90
Bronchopulmonary dysplasia ^a	26 (70%)	23 (69%)	3 (75%)	.99
Bronchopulmonary dysplasia, grade ^a				.76
I	11 (30%)	10 (30%)	1 (25%)	
II	4 (10%)	3 (9%)	1 (25%)	
III	11 (30%)	10 (30%)	1 (25%)	
Severe IVH (grade III/intraparenchymal hemorrhage)	6 (12%)	—	6 (35%)	<.001
Time of severe IVH diagnosis, days	3 (1–3)	—	3 (1–3)	—
Survival	37 (74%)	33 (100%)	4 (24%)	<.001
PMA on discharge, weeks ^a	41.6 ± 4.9	41.6 ± 4.8	41.5 ± 6.0	.96
Current weight on discharge, g ^a	3,365 ± 1,177	3,322 ± 1,158	3,662 ± 1,453	.59
Ventilation-free days	83.9 ± 20.1	84.2 ± 20.1	82.8 ± 21.4	.87
Stay, days ^a	116 (105–140)	113 (105–139)	140 (138–141)	.19

Continuous variables are expressed as mean ± SD or median (interquartile range). *P* values of Student *t* test or Mann–Whitney test. Categorical variables are expressed as *n* (%). *P* values of chi-square test or Fisher exact test.

^aData among survivors.

IVH, intraventricular hemorrhage; PMA, postmenstrual age.

A cutoff of a peak P_{aCO_2} <65 mm Hg, P_{aCO_2} fluctuation <25 mm Hg, and P_{aCO_2} deviation <15 mm Hg from the target had a sensitivity of 0.50, 0.67, and 0.50, respectively, and specificity of 0.82, 0.73, and 0.73, respectively, for absence of severe IVH (Table 5, Fig. 2A). Similarly, a cutoff of a peak P_{aCO_2} <65 mm Hg, P_{aCO_2} fluctuation <25 mm Hg, and P_{aCO_2} deviation <15 mm Hg from the target had a sensitivity of 0.50, 0.60, and 0.50, respectively, and specificity of 0.82, 0.73, and 0.73, respectively for survival (Table 5, Fig. 2B), and finally, a cutoff of a peak P_{aCO_2} <65 mm Hg, P_{aCO_2} fluctuation <25 mm Hg, and P_{aCO_2} deviation <15 mm Hg from the target had a sensitivity of 0.50, 0.57, and 0.57, respectively, and specificity of 0.87, 0.76, and 0.73, respectively for survival without severe IVH (Table 5, Fig. 2C).

Discussion

The findings of our study support that in extremely preterm neonates ventilated in first-intention HFJV, the initial respiratory stabilization, the timely administration of surfactant, and the fine-tuning of P_{aCO_2} levels within the first day of life are significantly associated with better outcomes. In this vulnerable cohort, peak P_{aCO_2} of <65 mm Hg, P_{aCO_2} fluctuations of <25 mm Hg, and P_{aCO_2} deviation from the target of <15 mm Hg are significantly associated with the absence of severe IVH, survival, and survival without severe IVH.

Our findings are in line with previously reported evidence that supports that deviation in CO_2 is significantly associated with serious intracranial consequences in neonates.^{21–25} Ambalavanan et al, in a secondary exploratory data analysis of 1316 extremely preterm infants of

Table 4. Multivariable logistic regression analysis of the association of survival or survival without severe intraventricular hemorrhage with the peak CO_2 , CO_2 fluctuation, and CO_2 deviation from target, adjusted for gestational age

	Absent severe IVH		Survival		Survival without severe IVH	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Peak CO_2	0.94 (0.88–0.99)	.048	0.93 (0.88–0.98)	.02	0.92 (0.88–0.980)	.008
Gestational age	1.24 (1.04–1.48)	.01	1.24 (1.07–1.44)	.003	1.23 (1.07–1.42)	.003
CO_2 fluctuation	0.93 (0.88–0.99)	.049	0.91 (0.86–0.97)	.008	0.91 (0.85–0.97)	.007
Gestational age	1.13 (1.05–1.23)	.001	1.14 (1.06–1.24)	.001	1.12 (1.04–1.20)	.001
CO_2 deviation from target	0.92 (0.84–0.98)	.045	0.90 (0.84–0.98)	.01	0.90 (0.83–0.97)	.01
Gestational age	1.12 (1.04–1.21)	.001	1.11 (1.05–1.19)	.001	1.09 (1.03–1.16)	.001

IVH, intraventricular hemorrhage; OR, odds ratio.

Table 5. The area under the receiver operating characteristic curve, sensitivity, and specificity of the peak CO₂ <65 mm Hg, CO₂ fluctuation <25 mm Hg, and CO₂ deviation <15 mm Hg from the target, for survival and survival without severe intraventricular hemorrhage

	Absent severe IVH			Survival			Survival without severe IVH		
	AUROC	Sensitivity	Specificity	AUROC	Sensitivity	Specificity	AUROC	Sensitivity	Specificity
Highest CO ₂ <65 mm Hg	0.735	0.50	0.82	0.671	0.50	0.82	0.708	0.50	0.87
CO ₂ fluctuation <25 mm Hg	0.760	0.67	0.73	0.732	0.60	0.73	0.706	0.57	0.76
CO ₂ deviation from the target <15 mm Hg	0.657	0.50	0.73	0.735	0.50	0.73	0.744	0.57	0.73

AUROC, area under the receiver operating characteristic; IVH, intraventricular hemorrhage.

extremely low birthweight from the large multi-center trial SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial), found an increased risk of bronchopulmonary dysplasia or death associated with higher peak, average, and fluctuation of P_aCO₂.²¹ Additionally, even at lower ranges of hypercapnia, the authors discovered that higher peak CO₂ was associated with a higher probability of neurological impairment/death and severe IVH/death, even when the severity of the illness was adjusted for.²¹ In several previous studies, CO₂ >54.8–60 mm Hg during the first days of life has been significantly associated with higher rates of severe IVH in very low and extremely low birthweight infants,^{23–25} whereas evidence supports that higher CO₂ fluctuation was a good indicator of severe IVH in very low and extremely low birthweight preterm infants.^{26,27} A prior study by Waitz et al demonstrated that the risk of severe IVH increased by 1.04 for every 0.98 mm Hg increase in P_aCO₂ in extremely preterm infants.²⁶ In addition, a study by Tamura et al established that fluctuations of end-tidal CO₂ levels during initial resuscitation of premature infants at birth were predictive of any IVH development with 96.5% sensitivity and 83.3% specificity.¹²

The theory beyond the impact of CO₂ on cerebral autoregulation indicates that CO₂ induces changes in cerebral vessels' tone and influences cerebral blood flow.^{28,29} Hypercapnia causes increased cerebral blood flow, which in turn causes cerebral edema, elevated intracranial pressure, and subsequent hemorrhage.³⁰ Significant fluctuations in CO₂ have already been described to be associated with neurodevelopmental morbidities, whereby fluctuations and extremely high or low values within the first few days after birth are associated with a higher risk of cerebral impairment.³¹ Recent research, however, indicates that the ischemia that results from hypocapnia is what causes a hemorrhage or an expansion of an existing hemorrhage after the ischemic zone has been reperfused.^{32,33}

Although the ideal P_aCO₂ target for clinical practice is still unknown, it might be advantageous to tolerate mild hypercapnia. Permissive hypercapnia is frequently utilized in the treatment of preterm newborns and can be induced to protect the lungs. However, when P_aCO₂ rises beyond 60 mm Hg, it can result in a 2-fold

increased risk of IVH,²² and when it rises above 75 mm Hg, it can result in a 5-fold increased risk of IVH.³⁴ According to a retrospective study, variations in P_aCO₂ can be a more significant risk factor for severe IVH than hypercapnia per se.²⁷

In our cohort, all extremely preterm neonates were ventilated with first-intention HFJV. Extremely preterm neonates are exceptionally vulnerable to volutrauma and lung shearing injury, which can be minimized by the use of jet tidal volumes smaller than physiologic dead space and the ability to effectively ventilate and oxygenate at relatively low mean airway pressures.^{14,18} A relative skepticism, however, persists because of the reported association of first-intention HFJV with significant adverse effects including IVH, cystic periventricular leukomalacia, and death in extremely preterm neonates.¹⁰ Previously, Wiswell et al, in a randomized controlled trial, examined the effect of hypotension, acidosis, hypoxemia, and hypocapnia during the first 3 days of life on the development of periventricular leukomalacia in premature neonates ventilated with HFJV and found that cumulative hypocapnia below a threshold level of 25 mm Hg during the first day of life was significantly associated with cystic periventricular leukomalacia.³⁵ In our study, we found no significant association of hypocapnia with cystic periventricular leukomalacia, possibly explained by the fact that our mean lowest CO₂ was 37.3 ± 9.1 mm Hg. Furthermore, similar trials conducted by Keszler et al⁹ and Carlo et al,³⁶ each found no significant increase in nonpulmonary morbidities for neonates in the HFJV cohort compared to the conventional ventilation group.

Limitations

It is important to recognize the limitations of our study. First, our single-center cohort study results might not be generalizable. Second, even though we collected many clinical variables and performed multivariable analysis in this retrospective analysis, we recognize that outcomes like IVH and survival are multifactorial, and we may have missed additional variables that might have influenced the outcomes of interest. Furthermore, our study does not address the impact of hypocapnia on brain injury

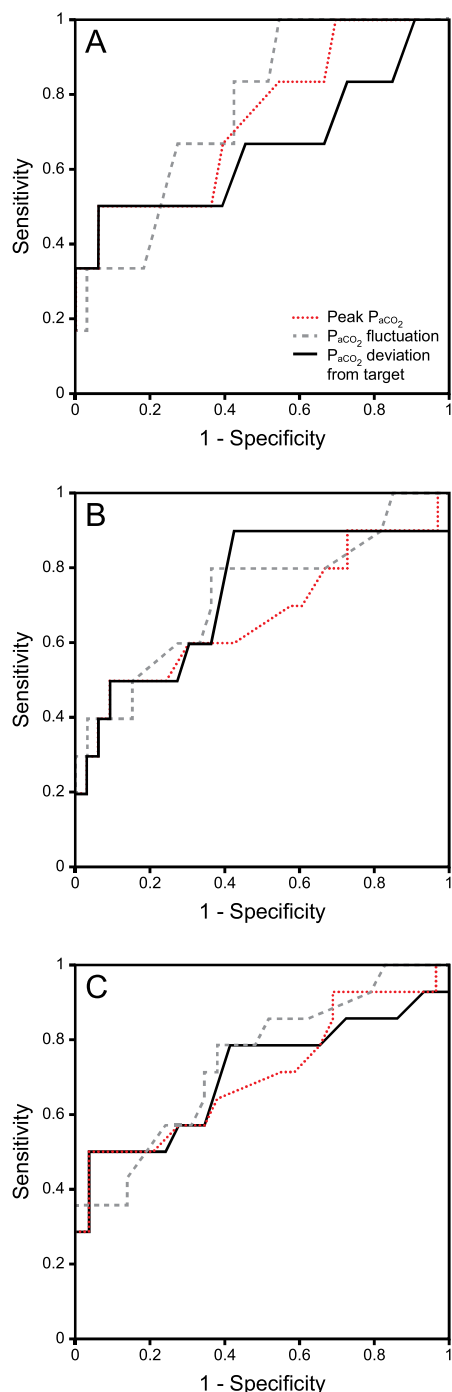


Fig. 2. Area under the receiver operating characteristic curves of the highest CO₂, CO₂ fluctuation, and CO₂ deviation from target (A) for absence of severe IVH, (B) survival, and (C) survival without severe IVH. IVH, intraventricular hemorrhage.

since there were no differences in the lowest P_{aCO_2} in our 2 groups, and there were no infants with periventricular leukomalacia in our cohort. Advanced monitoring including cerebral near-infrared spectroscopy will likely shed

more light on the impact of hypocapnia on cerebral perfusion. Because of the study's design, we were also unable to investigate how any ventilation strategies other than the initial first-intention approach affected the results that were assessed. Last, important P_{aCO_2} trends may have been missed by fixed interval monitoring as opposed to continuous monitoring.

Conclusions

In extremely preterm neonates ventilated with first-intention HFJV, the initial respiratory stabilization, the timely administration of surfactant, and the fine-tuning of P_{aCO_2} levels within the first day of life were significantly associated with better outcomes. In this vulnerable cohort, peak P_{aCO_2} of <65 mm Hg, P_{aCO_2} fluctuations of <25 mm Hg, and P_{aCO_2} deviation from the target of <15 mm Hg were significantly associated with survival, absence of severe IVH, and survival without severe IVH. Further prospectively designed studies are warranted to examine the optimal P_{aCO_2} thresholds in this vulnerable cohort to improve survival and optimize neurodevelopmental outcomes.

Ethics Approval and Consent to Participate

The study was approved by the institutional review board (Protocol Number 2023P001168/05.05.2023).

Author Disclosure Statement

The authors have no conflicts of interest relevant to this article to disclose.

Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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