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Influence of PCO_2 Control on Clinical and Neurodevelopmental Outcomes of Extremely Low Birth Weight Infants

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Abstract
Background: Levels or fluctuations in the partial pressure of CO_2 (PCO_2) may affect outcomes for extremely low birth weight infants. ***Objectives:*** In an exploratory analysis of a randomized trial, we hypothesized that the PCO_2 values achieved could be related to significant outcomes. ***Methods:*** On each treatment day, infants were divided into 4

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groups: relative hypocapnia, normocapnia, hypercapnia, or fluctuating PCO_2. Ultimate assignment to a group for the purpose of this analysis was made according to the group in which an infant spent the most days. Statistical analyses were performed with analysis of variance (ANOVA), the Kruskal-Wallis test, the χ^2 test, and the Fisher exact test as well as by multiple logistic regression. ***Results:*** Of the 359 infants, 57 were classified as hypocapnic, 230 as normocapnic, 70 as hypercapnic, and 2 as fluctuating PCO_2. Hypercapnic infants had a higher average product of mean airway pressure and fraction of inspired oxygen (MAP × FiO_2). For this group, mortality was higher, as was the likelihood of having moderate/severe bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and poorer neurodevelopment. Multiple logistic regression analyses showed an increased risk for BPD or death associated with birth weight ($p < 0.001$) and MAP × FiO_2 ($p < 0.01$). The incidence of adverse neurodevelopment was associated with birth weight ($p < 0.001$) and intraventricular hemorrhage (IVH; $p < 0.01$). ***Conclusions:*** Birth weight and respiratory morbidity, as measured by MAP × FiO_2, were the most predictive of death or BPD and NEC, whereas poor neurodevelopmental outcome was associated with low birth weight and IVH. Univariate models also identified PCO_2. Thus, hypercapnia seems to reflect greater disease severity, a likely contributor to differences in outcomes.

Introduction

Carbon dioxide, aside from being a byproduct of energy metabolism, is an important regulator for vascular tone and blood pH. In healthy subjects, the partial pressure of carbon dioxide (PCO_2) is controlled by spontaneous respiration to keep the pH close to 7.4, a level normally achieved with a PCO_2 of 40 mm Hg. Metabolic abnormalities that shift pH levels result in physiological alterations to respiratory drive and thus PCO_2. Furthermore, changing PCO_2 also affects kidney function, as bicarbonate is retained to move pH levels back to the physiological norm of 7.4. The effects of PCO_2 on organ function and perfusion differ from organ to organ. A higher PCO_2 (i.e., >40 mm Hg), may provide some protection for the myocardium [1] and increase pulmonary vascular tone, thus increasing pulmonary arterial pressure [2]. At the same time, central nervous system vascular tone is decreased, leading to brain hyperperfusion [3, 4], which may increase cerebral perfusion and oxygen delivery to the brain but also increases the risk of intraventricular hemorrhage (IVH) in very preterm infants, where extreme values have the greatest importance [5, 6]. At a low PCO_2, brain perfusion is reduced and blood supply to the brain may become compromised, possibly even resulting in cerebral palsy in newborns [4, 7]. Furthermore, PCO_2 affects the electrical activity of the brain [4, 8].

Important cellular functions are also influenced by PCO_2. Various animal models have demonstrated either protective or harmful effects. Lung epithelial cell membrane repair [9] and vectorial epithelial ion transport (alveolar fluid clearance) [10] were impaired by higher PCO_2 in in vitro models. Furthermore, young rats developed retinopathy when exposed to very high PCO_2 values (of approx. 100 mm Hg) [11]. Neuronal cells may be less susceptible in this aspect, but data on this are sparse.

Extremely preterm infants who survive intensive care are at a high risk of developmental abnormalities involving various organs, including the lungs, central nervous system, kidneys, and digestive system [12, 13]. Given its broad-ranging effects on various tissues, alterations in PCO_2 may have lasting effects on organ functions later in life [14].

In a recently completed clinical multicenter trial, infants were randomly allocated to 2 different PCO_2 target ranges [15]. Although both target ranges were in the hypercapnic range, there were distinct differences between them. Regardless of the randomized target group to which they were assigned, infants had a marked influence on PCO_2 levels through their own respiratory drive, maturity, and degree of lung disease, and did not always remain within the target range to which they had been assigned. This resulted in a considerable overlap in actual PCO_2 values between the study groups. Although the randomized assignment to a target group did not significantly influence important clinical outcomes, there were trends suggesting that the higher target range could be associated with an increased risk of bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) [15], but does not affect neurodevelopment [16]. Effects such as these may be more evident in analyses based on actual PCO_2 values rather than on the prescribed target ranges.

Extensive data on blood gas analyses and important clinical outcomes were collected during the trial [15]. We sought to determine whether PCO_2 during the first 2 weeks of life may influence the short- and long-term health of preterm infants. We hypothesized that different PCO_2 trajectories might be associated with different rates of adverse outcomes.

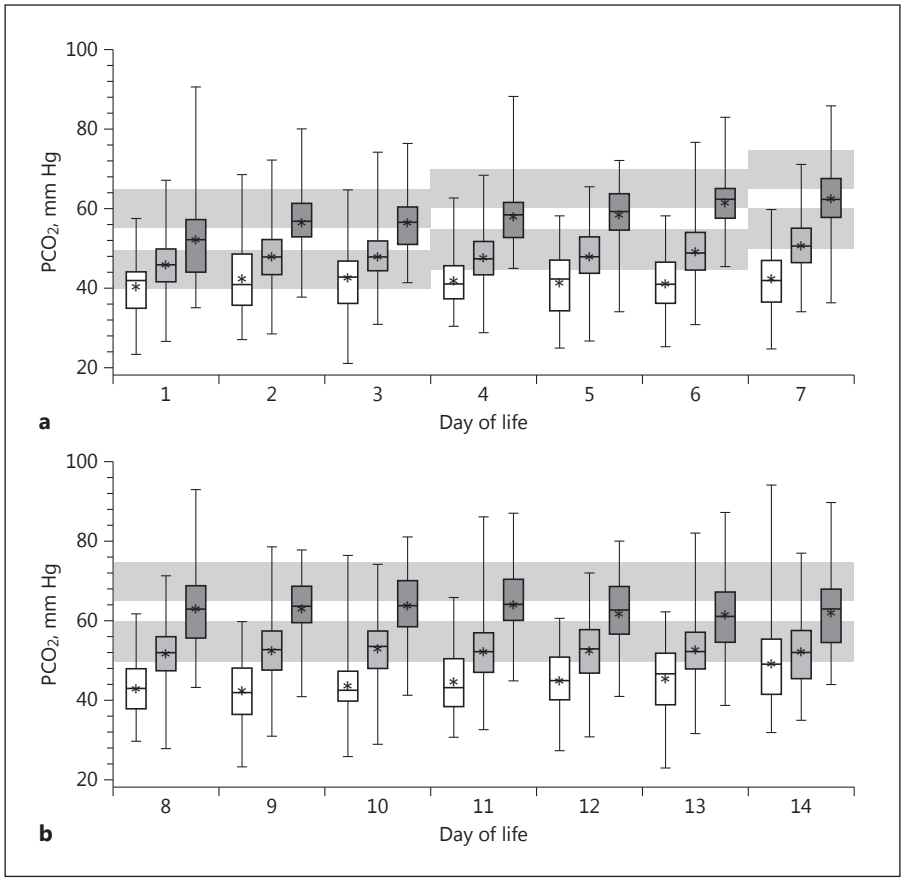

Fig. 1. Daily PCO_2 distributions of the 3 groups, shown as box-and-whisker plots. **a** Days 1–7. **b** Days 8–14. Boxes, 25th–75th percentile; whiskers, minimum – maximum. Inside the boxes, horizontal lines represent median values and asterisks represent mean values. White boxes, relatively hypocapnic group; light grey boxes, normocapnic group; darker grey boxes, relatively hypercapnic group. The shaded areas in the background indicate the PCO_2 target ranges of the former randomized trial [15].

Methods

Patient Allocation

Inborn infants with a gestational age of 23(0/7)–28(6/7) weeks, weighing 400–1,000 g and receiving endotracheal intubation and mechanical ventilation within 24 h of birth, were enrolled within 36 h of birth into the Permissive Hypercapnia in Extremely Low Birth Weight Infants (PHELBI) trial at 16 tertiary care perinatal centers in Germany between March 2008 and July 2012 [15]. Each center's institutional review board approved the trial and written informed consent was obtained from the parents or legal guardians of all of the infants.

The infants were randomly allocated to 2 different PCO_2 target ranges. These target ranges increased age-dependently in both groups to facilitate weaning, and were applied for the first 14 days of life or until extubation. A detailed description of the trial protocol has been published previously [15].

PCO_2 Variables

This data analysis was based on the actual PCO_2 values obtained by blood gas analyses during the first 14 days of life, rather than on the group to which infants were randomly assigned.

Infants were categorized into 4 groups according to their PCO_2 values, relative to those of other infants in the study. Because of their higher impact on outcome, the extreme PCO_2 values of each infant were used for assignment to a group, similar as in previous analyses [17, 18]. Every treatment day, the maximum PCO_2 values achieved by all infants were ranked into 4 quartiles. The same was done with the minimum PCO_2 values. Infants whose minimum PCO_2 was in the lowest quartile of the minimal quartiles but whose maximum PCO_2 did not reach the highest maximal quartile were defined as "hypocapnic." Infants whose minimum PCO_2 was not in the lowest minimal quartile but whose maximum PCO_2 was in the highest maximal quartile were defined as "hypercapnic." Infants whose minimum PCO_2 was in the lowest minimal quartile and whose maximum PCO_2 was in the highest maximal quartile were defined as "fluctuating," and the remainder, whose PCO_2 levels reached neither the lowest minimal nor highest maximal quartile, were considered "normocapnic." Assignment to a group for the purpose of data analysis was done on the basis of the category in which the infant spent the most days, and in the event of an equal number of days being spent in 2 categories, more weight was given to the earlier days.

We also calculated maximum, minimum, and time-weighted average PCO_2 exposure. Severity of lung disease was assessed by the product of mean airway pressure (MAP) and fraction of inspired oxygen (FiO_2).

Outcome Assessments

BPD was defined as requiring mechanical pressure support or supplemental oxygen at 36 weeks ± 2 days postmenstrual age, including an O_2 reduction test for infants requiring an FiO_2 <0.3

Table 1. Comparative demographic data, overall and by PCO_2 category

	All infants (n = 359)	Hypocapnic (n = 57, 16%)	Normocapnic (n = 230, 64%)	Hypercapnic (n = 70, 19%)	p
Gestational age, weeks[§]	25(4/7)±1(2/7)	25(6/7)±1(3/7)	25(5/7)±1(2/7)	25(2/7)±1(3/7)	0.06
Birth weight, g[§]	711±154	690±173	724±147	690±158	0.14
Male	204 (57)	27 (47)	130 (57)	46 (66)	0.11
Antenatal steroids (any)	319 (89)	51 (90)	203 (88)	63 (90)	0.91
PPROM >24 h	80 (22)	16 (28)	49 (21)	15 (21)	0.54
5-min Apgar[‡]	8 (1–10)	8 (4–10)	8 (1–10)	8 (1–10)	0.49
Surfactant[†]	347 (97)	55 (97)	222 (97)	68 (97)	1.00
First randomized into the high target group	179 (50)	25 (44)	99 (43)	53 (76)	<0.01
PDA	52 (15)	7 (13)	26 (11)	17 (27)	<0.01
Methylxanthine therapy[†]	337 (94)	54 (95)	220 (96)	62 (89)	0.10
VT_e, mL/kg[§]	5.44±1.85 (n = 204)	5.72±1.70 (n = 25)	5.45±1.94 (n = 129)	5.38±1.65 (n = 48)	0.75
PCO_2, mm Hg[§]	51±7	43±5	50±4	60±4	<0.01
pH[§]	7.28±0.06	7.32±0.05	7.29±0.05	7.23±0.05	<0.01
MAP × FiO_2[‡]	1.89 (0.82–16.91)	1.50 (0.85–9.28)	1.83 (0.82–16.91)	2.73 (1.39–11.25)	<0.01
CRIB score[‡]	7 (1, 4, 8, 16)	7 (1, 4, 9, 16)	6 (1, 4, 8, 15)	8 (1, 5, 9, 14)	<0.01

Two infants with mainly fluctuating PCO_2 values were not assigned to any group. They received no prenatal steroids and were initially randomized into the hypercapnic arm of the trial. Their MAP × FiO_2 values were 3.45 and 5.89, and their CRIB scores were 9 and 10.

Unless otherwise specified, data are given as: number of infants (%), χ^2 test. [§] Mean ± SD, 1-way ANOVA. [†] The Fisher exact test. [‡] Median (range), and for the CRIB score: median (minimum, 1st quartile, 3rd quartile, maximum), Kruskal-Wallis test.

PPROM, preterm premature rupture of membranes; PDA, patent ductus arteriosus; VT_e, expiratory tidal volume; CRIB, Clinical Risk Index for Babies.

[19]. This also represents moderate-to-severe BPD according to the National Institute of Child Health and Development consensus definition [20]. The incidence and severity of IVH were assessed according to the method of Papile et al. [21], by cranial ultrasound assessed by a single pediatric radiologist on the first day of life, at 12–14 days, and at 36 weeks postmenstrual age. Retinopathy of prematurity (ROP) was routinely screened and classified according to the international classification [22]. NEC was diagnosed when the clinical and radiological findings corresponded to stage II or higher according to the criteria of Bell et al. [23]. A ductus arteriosus was considered persistent if it persisted throughout the period of hospitalization or if it needed to be ligated after medical treatment failed. The Clinical Risk Index for Babies (CRIB) score was also determined [24].

All surviving infants were invited to a neurodevelopmental follow-up examination at 2 years ± 3 months corrected age [16]. The mental developmental index (MDI) and the psychomotor developmental index (PDI) were determined using the Bayley Scales of Infant Development II (German translation) [25]. Neurodevelopmental impairment was defined as either MDI <70 or PDI <70 or hearing or visual impairments. Furthermore, motor function was assessed by the modified Gross Motor Function Classification System (GMFCS), with scores ranging from level 0 (normal) to level 5 (the most impaired) [26]. Parent perception was assessed by the EFkE (Elternfragebogen zur kindlichen Entwicklung) questionnaire [27, 28], a validated German translation of the Child Development Inventory (CDI) [29].

Statistical Considerations

Statistical tests included the ANOVA, Kruskal-Wallis, χ^2, and Fisher exact tests as appropriate. All analyses have to be considered as secondary and hypothesis-generating since this investigation was not based on a randomized intervention. Adjustments for multiple testing were not done. A p value of <0.05 was considered significant. Univariate logistic regression analyses were performed to identify possible risk factors for adverse outcomes, including minimal, maximal, and average PCO_2 exposure, and the PCO_2 standard deviation. The adverse outcomes tested were mortality, BPD, ROP, NEC, severe IVH, MDI <70/PDI <70, neurodevelopmental impairment, or the end points mentioned combined with death. Risk factors that yielded significant differences in univariate analyses were fed into multiple logistic regression to determine which conditions constituted independent risk factors. SAS software v9.4 (SAS Institute, Cary NC, USA) was used throughout. The trial, from which these data were derived, was approved by the institutional review board of each center and registered as ISRCTN56143743.

Results

Of the 359 infants enrolled, 311 survived, and 265 of these participated in the follow-up exam. The remaining 46 were lost to follow-up for various reasons [16]. Demographic characteristics and clinical data up to discharge did not differ for infants with and without follow-up [16].

Table 2. Comparative clinical outcome data, overall and by PCO_2 category

	All infants (n = 359)	Hypocapnic (n = 57, 16%)	Normocapnic (n = 230, 64%)	Hypercapnic (n = 70, 19%)	p
Mortality until 36 weeks PMA	44 (12)	7 (12)	17 (7)	19 (27)	
Moderate-to-severe BPD	75 (21)	10 (18)	42 (18)	22 (31)	<0.01
Moderate-to-severe BPD or death	119 (33)	17 (30)	59 (26)	41 (59)	
BPD (cons. def.) mild†	216 (60)	35 (61)	153 (67)	28 (40)	
BPD (cons. def.) moderate†	41 (11)	7 (12)	23 (10)	11 (16)	<0.01
BPD (cons. def.) severe†	34 (10)	3 (5)	19 (8)	11 (16)	
Mortality until day 14§	28 (8)	7 (12)	10 (4)	11 (16)	<0.01
IVH (all grades)	104 (29)	10 (18)	73 (32)	20 (29)	<0.01
Severe IVH (grade 3–4)	47 (13)	7 (12)	29 (13)	11 (16)	0.01
Periventricular leukomalacia	27 (8)	5 (9)	15 (7)	6 (9)	0.76
Hydrocephalus internus	51 (17)	7 (15)	33 (16)	11 (22)	0.59
Hydrocephalus internus with shunt†	14 (4)	1 (2)	11 (5)	2 (3)	0.67
Postnatal steroids (any)	131 (36)	13 (23)	83 (36)	33 (47)	0.01
Postnatal dexamethasone	59 (17)	9 (16)	35 (15)	14 (21)	0.55
Postnatal hydrocortisone	88 (25)	6 (11)	55 (24)	25 (37)	<0.01
Retinopathy of prematurity	156 (47)	26 (50)	104 (47)	25 (46)	0.88
Severe retinopathy ≥ grade 3	46 (14)	6 (12)	30 (14)	10 (18)	0.57
Necrotizing enterocolitis ≥2†	28 (8)	6 (11)	12 (5)	9 (14)	0.04
Weight at 36 weeks PMA, g‡	1,958±350 (313)	1,892±310 (50)	1,997±353 (211)	1,869±353 (52)	0.02

The 2 infants with mainly fluctuating PCO_2 values were not assigned to any group; one died and the other survived with severe BPD. BPD corresponds to moderate or severe BPD according to the consensus definition (cons. def.) [20].

Unless otherwise specified, data are given as: number of infants (%), χ^2 test. † The Fisher exact test. ‡ Mean ± SD (n of patients contributing data), 1-way ANOVA. # These infants died before the final IVH grading was done.

PMA, postmenstrual age.

The majority of infants (64%) were classified as normocapnic, 16% were hypocapnic, and 19% were hypercapnic. Two infants were classified on most days as fluctuating, so we decided to not consider them and to perform the data analysis with 3 groups only. The daily PCO_2 ranges of the 3 groups are shown in Figure 1.

The baseline characteristics of infants in all 3 groups were similar (Table 1). Aside from higher PCO_2 and lower pH levels, hypercapnic infants had higher MAP × FiO_2, higher CRIB scores, and were more likely to have a patent ductus arteriosus (PDA). Tidal volumes were not statistically different between groups. Most infants in the hypercapnic group had initially been randomized into the hypercapnic arm of the main trial, but there was a considerable overlap with the other groups.

Hypercapnic infants had significantly higher mortality and incidence of moderate-to-severe BPD, were more likely to have received postnatal hydrocortisone and to develop NEC, and gained less weight (Table 2).

Interestingly, hypocapnic infants were less likely to have an IVH, when compared with all other groups.

There also appeared to be a relationship between neurodevelopmental outcomes and PCO_2 group (Table 3). Hypercapnic infants had significantly lower MDI scores and were more likely to have an MDI <70 and cerebral palsy by GMFCS scores (≥2). Their weight and height gains were lower. The PDI results, in contrast, were not affected. Furthermore, there were strong associations between the CRIB scores and major outcome variables (Table 4).

In the multiple logistic analyses, moderate-to-severe BPD or death was related to birth weight and MAP × FiO_2 (Table 5). The combined outcome, BPD/IVH/death, was only associated with MAP × FiO_2 (Table 6). Low MDI scores were associated with birth weight and IVH (Table 7) whereas low PDI scores were strongly associated with IVH (Table 8).

The outcome of the 2 mainly fluctuating infants was poor, despite the absence of a severe IVH. One died and the other survived with severe BPD and neurodevelopmental impairment, and did not achieve MDI and PDI scores >49.

Table 3. Comparative neurodevelopmental outcome data, overall and by PCO_2 category

	All infants (n = 265)	Hypocapnic (n = 42)	Normocapnic (n = 176)	Hypercapnic (n = 46)	p
MDI[§]	82 (49–120; 249)	86 (49–112; 39)	84 (49–120; 168)	64 (49–116; 41)	0.05
MDI <85	131/249 (53)	19/39 (49)	85/168 (51)	26/41 (63)	0.30
MDI <70	78/249 (31)	11/39 (28)	45/168 (27)	21/41 (51)	<0.01
PDI[§]	84 (49–114; 226)	88 (49–114; 33)	84 (49–114; 154)	83 (49–110; 38)	0.25
PDI <85	118/226 (52)	16/33 (49)	80/154 (52)	21/38 (55)	0.85
PDI <70	75/226 (33)	9/33 (27)	48/154 (31)	17/38 (45)	0.21
Total mortality at follow-up	48/359 (13)	7/57 (12)	20/230 (9)	20/70 (29)	<0.01
Hearing impairment[§]	13/263 (5)	1/40 (3)	8/177 (5)	3/45 (7)	0.67
Visual impairment	50/264 (19)	7/40 (18)	29/178 (16)	13/45 (29)	0.15
NDI (MDI <70 or PDI <70/hearing or visual impairment)	115/233 (49)	16/35 (46)	71/157(45)	27/40 (68)	0.04
NDI or death	163/281 (58)	23/42 (55)	91/177 (51)	47/60 (78)	<0.01
GMFCS[§]					
Level 0	133 (50)	18 (43)	92 (52)	23 (49)	
Level 1	89 (34)	19 (45)	61 (35)	9 (19)	
Level 2	17 (6)	3 (7)	6 (3)	8 (17)	0.01
Level 3	10 (4)	2 (5)	6 (3)	2 (4)	
Level 4	13 (5)	0 (0)	9 (5)	4 (9)	
Level 5	3 (1)	0 (0)	2 (1)	1 (2)	
CDI score[†]	22 (1–58; 188)	22 (8–58; 35)	22 (1–52; 116)	22 (1–46; 37)	0.24
Percentiles for CDI scores[‡]	10 (<2 to >90)	5 (<2 to >90)	10 (<2 to >90)	5 (<2 to >90)	
Weight at follow-up, kg[†]	10.5 (5.6–17.2; 254)	10.1 (7.7–17.2; 39)	10.8 (5.6–16.0; 171)	10.0 (6.7–14.9; 43)	0.01
Height at follow-up, cm[†]	84 (66–102; 253)	84 (73–93; 40)	85 (70–102; 170)	83 (66–92; 42)	0.01
Head circumference, cm[†]	47 (40–52; 253)	46.6 (42.5–49; 41)	47 (40–51; 168)	46 (43–52; 44)	0.11
Corrected age at follow-up, months[†]	24 (18–31; 265)	24 (20–29; 42)	24 (18–31; 176)	24 (19–28; 46)	0.14

The 2 infants with mainly fluctuating PCO_2 values were not assigned to any group; one died and the other survived but was severely impaired, with MDI <49 and PDI <49.

Unless otherwise specified, data are given as: n (%), median (range; n); χ^2 test. [§] The Fisher exact test. [†] The Kruskal-Wallis test. [‡] According to the standard sample: median (range).

MDI, mental developmental index; PDI, psychomotor developmental index; NDI, neurodevelopmental impairment; GMFCS, Gross Motor Function Classification System; CDI, Child Development Inventory.

Table 4. Relationship of CRIB scores with common adverse outcomes

Outcome	No	Yes	p
Death or BPD	5 (1, 4, 8, 15), n = 240	8 (1, 7, 9, 16), n = 119	<0.01
IVH (all grades)[†]	7 (1, 4, 8, 14), n = 227	6 (1, 5, 8, 15), n = 104	0.31
Death or BPD or IVH	5 (1, 4, 7, 14), n = 174	7 (1, 5, 9, 16), n = 185	<0.01
MDI <85	5 (1, 4, 7, 14), n = 118	7 (1, 4, 8, 14), n = 147	<0.01
PDI <85	5 (1, 4, 7, 14), n = 108	7 (1, 4, 8, 14), n = 157	0.01
MDI <70	5 (1, 4, 8, 14), n = 171	7 (1, 6, 8, 14), n = 94	<0.01
PDI <70	6 (1, 4, 8, 14), n = 151	7 (1, 4, 8, 14), n = 114	<0.01

BPD corresponded to moderate/severe BPD according to the consensus definition [20]. CRIB score: median (minimum, 1st quartile, 3rd quartile, maximum). The Wilcoxon rank sum test was used. CRIB, Clinical Risk Index for Babies.

[†] The CRIB scores of infants who died before the IVH could be finally evaluated were: 9.5 (4, 7.5, 10.5, 16), n = 28.

Table 5. Odds ratios for the risk of moderate-to-severe BPD or death using multiple logistic regression analysis

	Difference for odds ratio	Odds ratio (95% confidence interval)	*p*
Gestational age	1 week	0.95 (0.75–1.21)	0.68
Birth weight	1 g	0.996 (0.994–0.998)	<0.001
Sex	female/male	0.64 (0.36–1.13)	0.13
Average PCO_2 exposure	1 mm Hg/h	1.04 (0.98–1.11)	0.17
Minimum PCO_2	1 mm Hg	1.04 (0.99–1.09)	0.13
Maximum PCO_2	1 mm Hg	0.99 (0.96–1.01)	0.25
Number of days with fluctuating PCO_2	1	1.50 (0.90–2.50)	0.12
Exposure to MAP × FiO_2 (ventilatory intensity)	mbar/h	2.29 (1.52–3.45)	<0.001
PDA	yes/no	1.43 (0.69–2.95)	0.33

BPD corresponded to moderate or severe BPD according to the consensus definition [20].

Table 6. Odds ratios for the risk of the combined outcomes of moderate-to-severe BPD or IVH (any grade) or death using multiple logistic regression analysis

	Difference for odds ratio	Odds ratio (95% confidence interval)	*p*
Gestational age	1 week	0.87 (0.71–1.07)	0.19
Birth weight	1 g	0.999 (0.997–1.001)	0.38
Sex	female/male	0.84 (0.52–1.37)	0.49
Average PCO_2 exposure	1 mm Hg/h	1.01 (0.96–1.06)	0.81
Minimum PCO_2	1 mm Hg	0.97 (0.93–1.02)	0.20
Maximum PCO_2	1 mm Hg	1.01 (0.99–1.03)	0.54
Number of days with fluctuating PCO_2	1	0.76 (0.47–1.22)	0.25
Exposure to MAP × FiO_2 (ventilatory intensity)	mbar/h	2.25 (1.49–3.42)	<0.001
PDA	yes/no	1.75 (0.86–3.56)	0.12

BPD corresponded to moderate or severe BPD according to the consensus definition [20].

Discussion

In line with our hypothesis, adverse outcomes were not evenly distributed, but occurred with greater frequency in the hypercapnic group, i.e., infants whose maximum PCO_2 was in the highest quartile of maximum PCO_2 on most days. The 2 fluctuating infants also had poor outcomes. This finding aligns well with previously published findings indicating that high PCO_2 levels may be harmful [30]. In the main trial, there was a nonsignificant trend towards a higher likelihood of BPD in infants who had been randomized into the higher target group [15]. It is also consistent with animal [31–33] and cell culture [9, 10] experiments which indicated potential damage to be associated with high PCO_2 levels.

While receiving comparable tidal volumes, the hypercapnic group required higher MAP × FiO_2, indicating poorer lung compliance and increased dead-space ventilation. Regression analyses revealed that a high MAP × FiO_2 requirement was, along with birth weight, the most predictive for the 2 outcome combinations death/BPD and death/BPD/IVH. Apparently, infants who required high-pressure ventilation were unable to attenuate higher PCO_2 values by their own efforts. These infants were subsequently prone to developing chronic lung disease. These findings indicate that the degree of severity of an individual's lung disease was the main determinant for subsequently developing BPD; this was corroborated by the higher CRIB scores for the hypercapnic group and the 2 fluctuating infants. Therefore, high or fluctuating PCO_2

Table 7. Odds ratios for the risk of MDI <70 using multiple logistic regression analysis

	Difference for odds ratio	Odds ratio (95% confidence interval)	*p*
Gestational age	1 week	1.10 (0.86–1.40)	0.46
Birth weight	1 g	0.995 (0.993–0.998)	<0.0001
Sex	female/male	1.45 (0.81–2.60)	0.22
Average PCO_2 exposure	1 mm Hg/h	1.03 (0.97–1.10)	0.32
Minimum PCO_2	1 mm Hg	0.97 (0.92–1.03)	0.32
Maximum PCO_2	1 mm Hg	1.02 (0.99–1.04)	0.17
Number of days with fluctuating PCO_2	1	0.91 (0.53–1.58)	0.75
Exposure to MAP × FiO_2 (ventilatory intensity)	mbar/h	1.28 (0.78–2.10)	0.33
IVH	yes/no	2.53 (1.35–4.75)	0.004

All factors listed in this table were shown to be statistically significant using univariate regression analysis.

Table 8. Odds ratios for the risk of PDI <70 using multiple logistic regression analysis

	Difference for odds ratio	Odds ratio (95% confidence interval)	*p*
Gestational age	1 week	1.12 (0.89–1.41)	0.34
Birth weight	1 g	0.998 (0.996–1.000)	0.12
Sex	female/male	0.91 (0.53–1.57)	0.74
Average PCO_2 exposure	1 mm Hg/h	1.00 (0.94–1.06)	0.98
Minimum PCO_2	1 mm Hg	0.96 (0.91–1.01)	0.08
Maximum PCO_2	1 mm Hg	1.02 (1.00–1.05)	0.05
Number of days with fluctuating PCO_2	1	0.80 (0.47–1.35)	0.40
Exposure to MAP × FiO_2 (ventilatory intensity)	mbar/h	1.38 (0.86–2.23)	0.19
IVH	yes/no	2.79 (1.54–5.04)	0.0007

All factors listed in this table were shown to be statistically significant using univariate regression analysis.

values may not be causally involved in the subsequent development of BPD. The large overlap between the PCO_2 groups and the initial randomized assignment to a group highlights the difficulty in maintaining preterm infants, who have a range of illnesses of varying severity and respiratory effort, within certain target ranges.

The significantly lower MDI scores in the hypercapnic group may suggest that poorer neurodevelopmental outcomes may be associated with a higher PCO_2 level. A similar association between high or fluctuating PCO_2 with IVH and neurodevelopmental delays have been found in single-center retrospective studies [6, 17]. Two previous randomized trials on permissive hypercapnia did not, however, reveal an association between randomized group assignment and neurodevelopmental outcome [15, 34], but a third trial demonstrated a significant increase in low MDI scores or death associated with hypercapnia [30]. Although this result was derived from a secondary outcome and the trial was small, it parallels the findings presented here, especially as the same component of the Bayley test (MDI) was affected.

Our multiple logistic regression analysis did not support a significant association between PCO_2 exposure and poor MDI or PDI scores. Poor MDI scores were associated with birth weight and IVH, and poor PDI scores with IVH only, as seen in previous studies [16, 35, 36].

The role of lung disease was also indicated by the association of poor MDI and PDI scores with higher CRIB scores. More severe lung disease may therefore be the most plausible link to neurodevelopmental outcomes,

since there is a clear, established association between BPD and poor development [14]. Lung disease has also been shown to adversely affect brain integrity in animal experiments [37].

SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) enrolled 1,316 infants and randomized them to receive continuous positive airway pressure (CPAP) with an upper PCO_2 limit of 65 mm Hg for intubation and extubation, with a strategy of using primary intubation, surfactant administration, and an upper PCO_2 limit of 50 mm Hg [38]. PCO_2 data were also available and were analyzed in relation to clinical outcomes [18]. A higher PCO_2 was clearly associated with death, BPD, IVH, and neurodevelopmental impairment. This may result from the much larger sample size, enabling even weaker associations to be recognized. It was postulated, as in our study, that high PCO_2 is a marker of disease severity.

In comparing this and previous analyses of the associations between PCO_2 and clinical outcomes [6, 17, 18], it is important to note the varying definitions used to divide infants into PCO_2 groups. In a first step, infants were classified according to their PCO_2 values on each treatment day and then ultimately assigned according to the most days spent in a category. This was done to avoid, for example, the classification of an otherwise stable infant with only 1 very high PCO_2 value on day 12 as hypercapnic or fluctuating. Such an infant would be very different from one with a high PCO_2 on each of the first 7 days of life. Our classification resulted in lower proportions of infants being classified hypocapnic, hypercapnic, or fluctuating, but our classification was strong as it was based on a consistent status over a number of days (Fig. 1). Regardless of this definition, however, the major findings of previous studies and ours were similar.

Limitations of this study include the retrospective design, based on a dataset from a trial that was not designed for this analysis, and the sample size which was not powered for the outcome parameters investigated. Therefore, type I and type II errors cannot be excluded, and all findings must primarily be seen as hypothesis-generating. Finally, a number of univariate and multiple analyses were performed, increasing the likelihood of random differences. The implications of the follow-up rate and the use of the German Bayley II translation have been discussed elsewhere [16].

In summary, infants with the highest and longest-lasting levels of PCO_2 tended to be those with the worst lung disease. Higher rates of mortality and BPD are therefore probably more related to worse lung disease at the beginning than PCO_2 values. PCO_2 can thus be viewed as a proxy of lung disease severity. It can be assumed that these infants were those least able to compensate for reductions in mechanical ventilatory support by their own respiratory efforts. The infants in the hypercapnic group were also found to have lower MDI scores, but this association was not reproducible in multiple linear regression analyses. Rather, birth weight and IVH were the strongest predictors of neurodevelopmental outcome. Our data do not allow us to recommend certain PCO_2 target ranges as desirable for ventilated preterm infants. As noted previously, PCO_2 targets for ventilated preterm infants should be tailored to optimize short-term outcomes [15, 16, 34].

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Disclosure Statement

The authors declare that they have no competing interests relevant to this article.

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