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Impact of Carbon Dioxide on Cerebral Oxygenation and Vital Parameters in Stable Preterm and Term Infants Immediately after Birth

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Keywords
Preterm infants · Transition · Near-infrared spectroscopy · Regional cerebral oxygen saturation · Carbon dioxide

Abstract
Introduction: Carbon dioxide (pCO_2) induces changes in the tone of cerebral vessels. The aim of the present study was to evaluate the impact of pCO_2 on cerebral regional tissue oxygen saturation ($crSO_2$), cerebral fractional tissue oxygen extraction (cFTOE), and cerebral tissue oxygen extraction (cTOE), measured with near-infrared spectroscopy (NIRS), in preterm and term infants 15 min after birth. ***Methods:*** Post hoc analyses of secondary outcome parameters of prospective observational studies were performed. Stable preterm and term infants with cerebral NIRS monitoring (INVOS 5100C) until minute 15 after birth and a blood gas analysis, performed between minutes 14–18 after birth, were included. Heart rate (HR) and arterial oxygen saturation (SpO_2) were recorded. pCO_2 was correlated with $crSO_2$, cFTOE, cTOE, SpO_2, HR, and partial pressure of oxygen (pO_2). ***Results:*** Eleven preterm infants with a median (IQR) gestational age of 34.8 (32.7–36.1) weeks were analyzed. Mean ± SD pCO_2 was 53.5 ± 4.2 mm Hg. At minute 15 after birth, $crSO_2$ was 82.6 (74.3–91.3)%, cFTOE 0.15 ± 0.09, cTOE 14.6 ± 8.4%, SpO_2 97.4 ± 2.1%, and HR 152 (136–167) bpm. pCO_2 correlated negatively with $crSO_2$ ($p = 0.012$) and positively with cFTOE ($p = 0.035$) and cTOE ($p = 0.037$). Eighty-four term infants with a gestational age of 39.0 (38.5–38.9) weeks were analyzed. pCO_2 was 53.5 ± 6.3 mm Hg. At minute 15 after birth, $crSO_2$ was 84.4 (80.8–85.1)%, cFTOE 0.14 ± 0.08, cTOE 13.6 ± 7.9%, SpO_2 96.5 ± 2.6%, and HR 155 (153–163) bpm. pCO_2 did only negatively correlate with pO_2 ($p = 0.034$) in term infants. ***Conclusion:*** In preterm infants, higher pCO_2 was associated with lower $crSO_2$ and higher cFTOE/cTOE. In term infants, no associations were observed. The present findings suggest that the vasodilatative effect of pCO_2 is less pronounced in preterm infants during immediate postnatal transition.

Introduction

Carbon dioxide (pCO_2) is one of the most potent mediators of cerebral autoregulation inducing changes in cerebral vessels' tone and influencing cerebral blood flow (CBF) [1, 2]. Cerebral autoregulation enables constant

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CBF, independent of changes in cerebral perfusion pressure as long as the blood pressure range is within the autoregulatory plateau [3]. Above the autoregulatory plateau, CBF increases and below, CBF decreases in a pressure-passive manner [4]. An impaired autoregulation leads to linear changes of CBF depending on changes in blood pressure [5]. An increase in pCO_2 attenuates CBF autoregulation. Higher pCO_2 is associated with cerebral vasodilatation and an increase in CBF, while a reduction in pCO_2 leads to cerebral vasoconstriction and a decrease in CBF [6, 7]. Significant fluctuations in pCO_2 have already been described to be associated with neurodevelopmental morbidities, whereby fluctuations and extreme high or low values within the first few days after birth are associated with a higher risk of cerebral impairment [8, 9].

Cerebral regional tissue oxygen saturation ($crSO_2$) can be monitored by continuous noninvasive measurements of oxygenated (HbO_2) and deoxygenated hemoglobin (Hb) using near-infrared spectroscopy (NIRS) [10, 11]. Near-infrared light propagates through tissue, and certain wavelengths are differently absorbed by HbO_2 and Hb [12]. Cerebral fractional tissue oxygen extraction (cFTOE) and cerebral tissue oxygen extraction (cTOE) can be calculated out of $crSO_2$ and arterial oxygen saturation (SpO_2).

Monitoring of cerebral oxygenation with NIRS in the delivery room during the immediate fetal-to-neonatal transition period is well established [13, 14]. Low cerebral oxygenation during immediate transition is associated with cerebral injury [15], whereby cerebral oxygenation can be improved by using NIRS monitoring and dedicated interventions [16]. However, knowledge of influencing parameters on cerebral oxygenation during immediate uncomplicated transition is still limited. Metabolic parameters like blood glucose [17] and circulatory parameters like ductus arteriosus and persistent foramen ovale have been demonstrated to influence cerebral oxygenation [18, 19]. However, so far, there are no investigations on the potential influence of pCO_2 on $crSO_2$, cFTOE, and cTOE in stable infants during the immediate transition after birth – within the first 15 min after life.

The aim of the present study was therefore to evaluate the potential correlation between pCO_2 and $crSO_2$, cFTOE, and cTOE (measured with NIRS), with routine monitoring parameters (SpO_2, heart rate [HR], mean arterial blood pressure [MABP], and rectal body temperature), with partial pressure of oxygen (pO_2), and with blood glucose in preterm and term infants without medical support 15 min after birth. We hypothesized that higher pCO_2 values would be associated with higher $crSO_2$ and lower cFTOE and cTOE values 15 min after birth due to increased CBF as a result of vasodilatation, with a weaker effect in preterm infants due to their more immature autoregulation.

Materials and Methods

Design

In the present study, a post hoc analysis of secondary outcome parameters of prospective observational studies, conducted at the Division of Neonatology, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Austria, between July 2009 and September 2018, was performed. The studies were approved by the Regional Committee on Biomedical Research Ethics (EC Nos. 19-291 ex 07/08, 23-403 ex 10/11, and 27-465 ex 14/15). Written parental informed consent was obtained before birth and inclusion in each study.

Inclusion and Exclusion Criteria

Preterm and term infants delivered by caesarean section, who received cerebral NIRS monitoring during the first 15 min after birth as participants of one of the prospective observational studies, were included. Furthermore, for inclusion into the present post hoc analysis, a heel-stick blood sample for blood gas and hemoglobin analysis was required. This had to be performed within 14–18 min after birth at the discretion of the respective attending neonatologist, to correlate the results with the NIRS and routine monitoring parameters at minute 15 after birth. Exclusion criteria were major congenital malformations and the need for supplemental oxygen and/or (non-)invasive respiratory support.

Monitoring

Antepartum medical histories were collected, and demographic data including gestational age, birth weight, sex, umbilical artery pH, Apgar scores, Hb concentration, and fetal hemoglobin (HbF) concentration were documented. Cord clamping was routinely delayed for 30 s after birth. Infants were dried and placed in the supine position under an overhead heater. The NIRS sensor was fixed on the left frontoparietal head using a modified CPAP cap or an elastic gauze bandage immediately after birth. NIRS measurements ($crSO_2$) were performed with the INVOS 5100C Cerebral/Somatic Oximeter Monitor (Medtronic, Minneapolis, MN, USA) with a neonatal transducer. Pulse oximetry was applied on the infants' right hand or wrist. SpO_2 and HR were measured with the IntelliVue MP30 monitor (Koninklijke Philips, The Netherlands). The monitoring was performed continuously during the first 15 min after birth. cFTOE and cTOE were calculated out of SpO_2 and $crSO_2$ by the following formulas: $cFTOE = (SpO_2 - crSO_2)/SpO_2$ and $cTOE = SpO_2 - crSO_2$ [20].

For noninvasive blood pressure measurements (IntelliVue MP50 monitor; Koninklijke Philips, The Netherlands) at minute 15 after birth, the pneumatic cuff was placed on the infants' right upper arm. Rectal body temperature was routinely measured once in minute 15 after birth.

All variables were stored in the multichannel system alpha trace digital MM (BESTMedical Systems, Vienna, Austria) for subsequent analysis. For the present study, mean values of $crSO_2$, SpO_2, and HR

Table 1. Demographic data and routine monitoring parameters

Demographic data	Preterm infants (n = 11)	Term infants (n = 84)	p value
Gestational age, weeks	34.8 (32.7–36.1)	39.0 (38.5–38.9)	<0.001*
Birth weight, g	2,101±370	3,145±441	<0.001*
Female sex	7 (64)	35 (42)	0.171
Umbilical artery pH	7.27 (7.23–7.32)	7.32 (7.30–7.32)	0.005*
Apgar 1 min	9 (9–9)	9 (9–9)	0.549
Apgar 5 min	10 (10–10)	10 (10–10)	0.194
Apgar 10 min	10 (10–10)	10 (10–10)	0.716
NIRS parameters			
$crSO_2$, %	82.6 (74.3–91.3)	84.4 (80.8–85.1)	0.398
cFTOE	0.15±0.09	0.14±0.08	0.615
cTOE, %	14.6±8.4	13.6±7.9	0.693
Routine monitoring			
SpO_2, %	97±2	97±3	0.201
HR, bpm	152 (136–167)	155 (153–163)	0.661
MABP, mm Hg	46 (40–50)	45 (45–50)	0.276
Blood pressure systolic, mm Hg	62 (59–68)	62 (55–66)	0.936
Blood pressure diastolic, mm Hg	34 (31–39)	36 (32–44)	0.365
Rectal body temperature, °C	36.8±0.4	37.0±0.3	0.045*
Partial pressure of pCO_2 and pO_2, mm Hg			
pCO_2	53.5±4.2	53.5±6.3	0.774
pO_2	45.3±9.2	41.0±5.4	0.196
Hemoglobin			
Hb, g/dL	18.9±2.5	18.9±1.7	0.896
HbF, %	77.8±5.8	72.2±5.7	0.011*
Blood glucose and pH			
Glucose mg/dL	50.5 (46.5–57.5)	50.0 (49.1–53.3)	0.774
pH	7.29±0.04	7.29±0.04	0.942

Data are presented as mean ± SD, median (IQR), or n (%). NIRS, near-infrared spectroscopy; $crSO_2$, cerebral regional tissue oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; cTOE, cerebral tissue oxygen extraction; SpO_2, arterial oxygen saturation; HR, heart rate; MABP, mean arterial blood pressure; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; Hb, hemoglobin; HbF, fetal hemoglobin. * p value indicates significant difference between preterm and term infants.

obtained during a 60-s period at minute 15 after birth were analyzed. Values of SpO_2 and HR were stored every second, whereby the sampling rate for $crSO_2$ was 8 s. As a quality criterion, values of $crSO_2$ and SpO_2 were eliminated when $crSO_2$ was higher than SpO_2.

Blood Analysis

pCO_2, pO_2, Hb, HbF, glucose values, and pH were obtained from capillary blood (ABL 800 Flex; Fa. Drott, Wiener Neustadt, Austria) according to the local standard operating procedures.

Statistical Analysis

Demographic, NIRS, and routine monitoring data are presented as n (%), mean and standard deviation, or median and interquartile range, as appropriate. Comparisons of categorical baseline characteristics (pCO_2, demographic and monitoring data, and results of blood analyses) between preterm and term infants were performed using the χ^2 test and for continuous variables using the t test or Mann-Whitney U test, as appropriate. Correlation analyses between pCO_2 and NIRS parameters ($crSO_2$, cFTOE, and cTOE), clinical routine monitoring parameters (SpO_2, HR, MABP, and rectal temperature), pO_2, and blood glucose were calculated separately for preterm and term infants using Pearson correlation for normally distributed data and the Spearman's rank correlation for not normally distributed data.

A p value <0.05 was considered statistically significant. These values were considered in an explorative sense; therefore, no multiple testing corrections were performed. Statistical analyses were performed using SPSS Statistics 24 (IBM, Armonk, NY, USA).

Results

A total of 148 preterm and 511 term infants, who were included in the prospective observational studies, were eligible. Eleven preterm and 84 term infants were

Table 2. Correlations between pCO_2 and NIRS parameters, routine monitoring parameters, pO_2, and blood glucose in preterm and term infants

	Preterm infants			Term infants		
	pCO_2			pCO_2		
	n	*r*	*p* value	*n*	*r*	*p* value
NIRS parameters						
$crSO_2$ (%)	11	−0.720	0.012*	84	0.028	0.801
cFTOE	11	0.636	0.035*	84	−0.008	0.946
cTOE (%)	11	0.632	0.037*	84	0.001	0.993
Routine monitoring						
SpO_2 (%)	11	−0.389	0.237	84	0.113	0.307
HR (bpm)	11	0.442	0.174	84	−0.184	0.094
MABP (mm Hg)	11	0.484	0.131	84	−0.044	0.697
Rectal body temperature (°C)	11	0.050	0.884	84	−0.179	0.113
Partial pressure of oxygen						
pO_2 (mm Hg)	11	−0.321	0.335	82	−0.235	0.034*
Blood glucose						
Glucose (mg/dL)	10	0.407	0.243	79	−0.022	0.847

NIRS, near-infrared spectroscopy; $crSO_2$, cerebral regional tissue oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; cTOE, cerebral tissue oxygen extraction; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SpO_2, arterial oxygen saturation; HR, heart rate; MABP, mean arterial blood pressure. **p* value indicates significant difference.

finally included in the present observational study (shown in Fig. 1). Demographic data, NIRS and routine monitoring parameters, and results of the blood gas analysis of the included preterm and term infants are summarized in Table 1. Correlation analyses are presented in Table 2.

Capillary blood gas samples were taken at a median (interquartile range) of 16.5 (15.5–17.2) and 16.0 (15.9–16.5) minutes after birth in preterm and term infants, respectively. No differences were observed between preterm and term infants in NIRS parameters, pCO_2, pO_2 Hb, blood glucose, and pH. HbF was significantly higher in preterm compared to term infants (shown in Table 1). In routine monitoring, no statistically significant differences between preterm and term infants were observed except for rectal body temperature.

In preterm infants, pCO_2 correlated significantly negatively with $crSO_2$ and positively with cFTOE and cTOE. Furthermore, in other parameters, no correlation with pCO_2 was observed (shown in Fig. 2a–d; Table 2).

In term infants, pCO_2 did not correlate with $crSO_2$, cFTOE, cTOE, SpO_2, HR, MABP, rectal temperature, or blood glucose. However, pCO_2 correlated significantly negatively with pO_2, nevertheless with only a weak correlation (shown in Fig. 2e–h; Table 2).

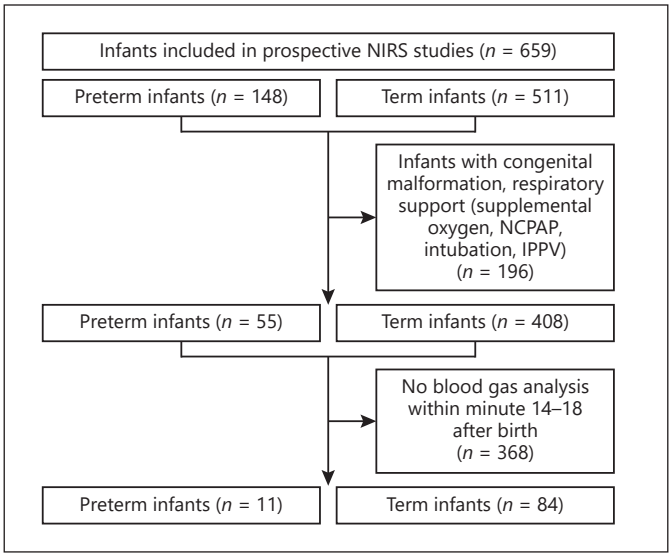

Fig. 1. Study flowchart showing the number of included and excluded preterm and term infants. NIRS, near-infrared spectroscopy.

Discussion

To our knowledge, this study is the first that analyzed potential correlations between pCO_2 and cerebral oxygenation during the immediate fetal-to-neonatal transi-

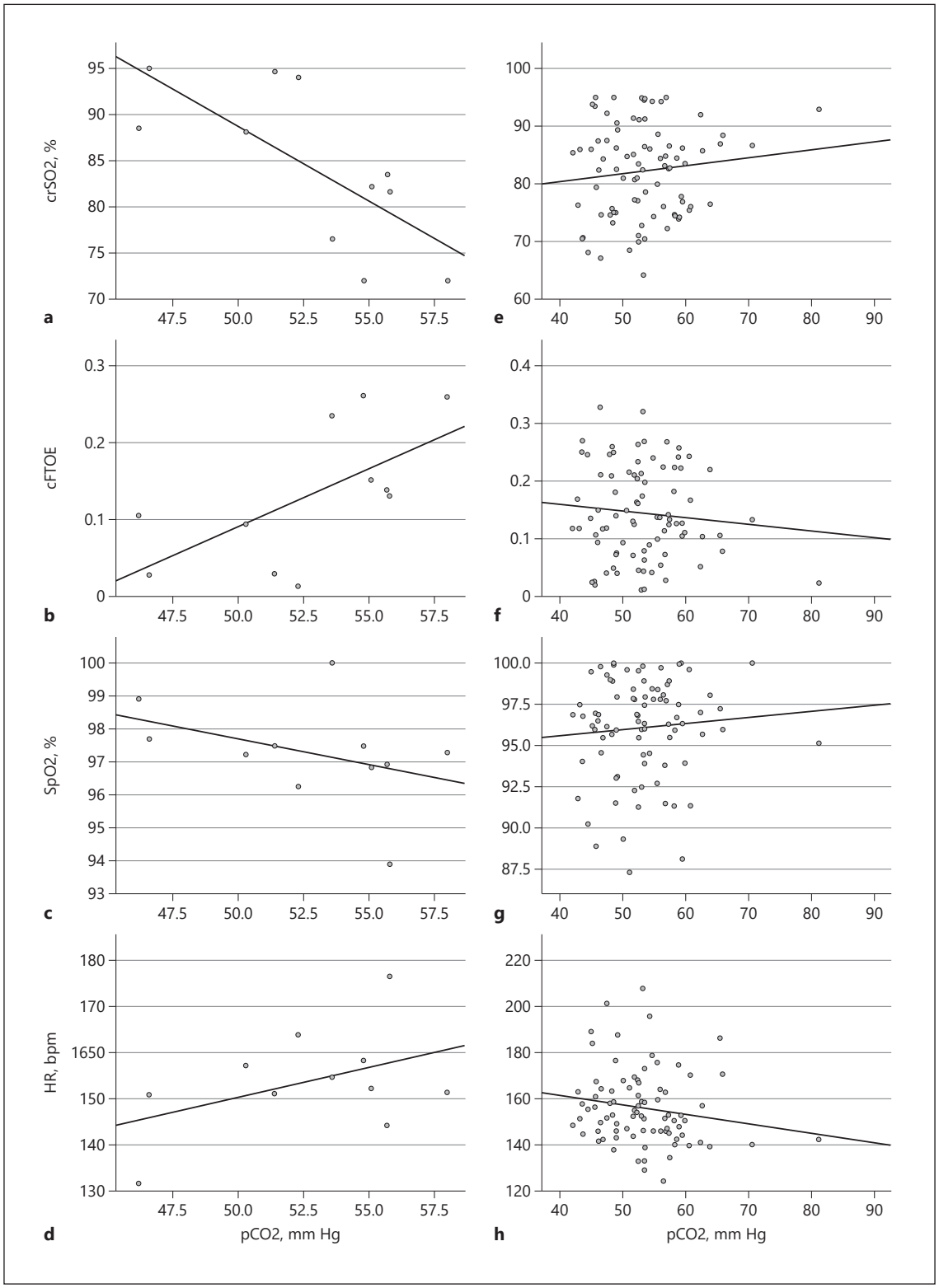

Fig. 2. Correlations of blood gas pCO_2 and NIRS monitoring parameters ($crSO_2$ and cFTOE), routine parameters (SpO_2 and HR), and gestational age in 11 preterm infants (**a–d**) and 84 term infants (**e–h**). pCO_2, partial pressure of carbon dioxide; NIRS, near-infrared spectroscopy; $crSO_2$, cerebral regional tissue oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; SpO_2, arterial oxygen saturation; HR, heart rate.

tion period in stable preterm and term infants. We showed that in preterm infants, pCO_2 values correlated negatively with $crSO_2$ and positively with cFTOE and cTOE, whereas no such correlation was observed in term infants. Furthermore, in preterm infants, a trend to positive correlation of pCO_2 with HR and MABP was observed. In term infants, there was no correlation between pCO_2 and routine monitoring parameters.

Previous studies reported pCO_2 values of 49–76 mm Hg at birth, with a decrease to 46–57 mm Hg within the first 10 min after birth [21]. In our study, pCO_2 values at 15 min after birth were within these ranges.

Correlations between pCO_2 and cerebral oxygenation were more pronounced in preterm infants compared to term infants. However, the direction of the correlation in preterm infants was not as we expected, as contrary to our hypothesis, higher pCO_2 values were associated with lower $crSO_2$ and higher cFTOE and cTOE values in preterm and term infants 15 min after birth. There are several hypotheses to explain these findings.

First, in the present study, preterm infants with higher pCO_2 values showed a trend to lower SpO_2 and pO_2 values in minute 15 after birth. SpO_2 and pO_2 influence $crSO_2$, cFTOE, and cTOE because oxygen delivery to the brain depends on SpO_2 and pO_2. Thus, lower SpO_2 and pO_2 values are associated with lower $crSO_2$ and higher cFTOE and cTOE values. The association of lower pO_2 with higher pCO_2 might be explained by a prolonged pulmonary transition due to reduced aeration of the lungs even in clinically stable infants showing lower SpO_2 values, though within normal ranges.

Second, immediately after birth, both pCO_2 and pO_2 are potent mediators for changes in cerebral vascular resistance. The strong vasodilatory influence of high pCO_2 values is a well-known phenomenon. In spontaneously breathing preterm infants 2 and 3 h after birth, the pCO_2-CBF reactivity has already been demonstrated by Pryds et al. [22], whereby CBF is well regulated within normal ranges of pCO_2 values. A similar effect of pCO_2 on CBF was observed in preterm infants in need for mechanical respiratory support within the first 3 days after birth [7]. Changes of CBF are described to be between 10% and 30% per kPa of pCO_2 in very preterm infants after immediate transition [23]. However, besides pCO_2, pO_2 is one of the most potent mediators inducing changes in the tone of the cerebral vessel and influences cerebral autoregulation and CBF. Below a pO_2 threshold of approximately 50 mm Hg, an increase in pO_2 has a strong vasoconstrictive effect on cerebral vessels [24]. pO_2 levels usually increase from 15–20 mm Hg to 46–57 mm Hg within the first 10 min after birth [25]. The vasoconstrictive effect of the pO_2 increases during immediate transition, up to minute 15 after birth, potentially may have outweighed the vasodilatative effect of higher pCO_2 values [6]. A decrease in pCO_2 values is further associated with a decrease in CBV in preterm and term infants within the first minutes after birth [24]. In summary, the present findings suggest that in preterm infants, the vasodilatative effect due to hypercarbia does not outweigh the vasoconstrictive effects of the increasing pO_2 values after birth.

In addition, in both preterm and term infants, higher pCO_2 levels were associated with lower pO_2 levels reaching significant negative correlation only in term infants. These associations suggest lower $crSO_2$ levels with higher pCO_2 due to the lower pO_2 as observed in preterm infants. In term infants, however, higher pCO_2 associated with lower pO_2 was not associated with $crSO_2$ suggesting that the vasodilatative effect of pCO_2 increased CBF to maintain oxygen delivery to the brain.

Third, in the present study, preterm infants had higher HbF levels compared to term infants. Higher HbF concentrations lead to a left shift of the oxygen dissociation curve (ODC), causing an increased affinity for oxygen (O_2) [26] that might also explain the different findings in the 2 groups [27]. At birth, there is a predominance of HbF, with a higher total amount in preterm infants compared to term infants. However, HbF is associated with reduced unloading of oxygen to tissue [28]. In the present study, the higher HbF in preterm infants results in ODC shift to the left causing a higher affinity of hemoglobin to oxygen, which may have partially antagonized the right shift of the ODC because of the higher pCO_2. This may especially explain the increase of cFTOE and cTOE with increasing pCO_2 values. Besides HbF, the metabolic parameter blood glucose has already been described to correlate negatively with $crSO_2$ [18]. In the present study, however, there was neither a difference in blood glucose levels between preterm and term infants nor a correlation between pCO_2 and blood glucose that might have confounded the present findings.

Fourth, cerebral oxygenation is dependent on oxygen delivery to the brain which is influenced by cardiac output and blood flow in the large arteries. The cardiac output and blood flow in large arteries is influenced by stroke volume, HR, and shunts. HR showed a nonsignificant positive correlation with pCO_2 in preterm infants that would suggest a higher cardiac output. However, since no echocardiography was performed, without information on stroke volume/myocardial function and

especially on intra- and extracardial shunts, we cannot rule out cardiac output clearly. During the immediate postnatal transition period, the closure of the ductus arteriosus and foramen ovale leads to changes in the direction of the blood flow. In term infants, the closure of the ductus arteriosus starts immediately after birth, but it is completely closed in most term infants within 48–72 h after birth [29]. The influence of an open ductus arteriosus and foramen ovale on cerebral oxygenation plays an important role during postnatal transition [18]. Baik et al. [19] observed that the sum of ductus arteriosus and foramen ovale diameter correlated negatively with cerebral oxygen saturation due to higher left-to-right shunt volume in term infants. Furthermore, higher shunt volumes due to the ductus arteriosus and foramen ovale lead to more pronounced left-to-right steal phenomena. A comparable finding has been described by Fuchs et al. [30] in very-low-birth-weight infants, reporting that oxygen delivery to the brain depends on cardiac output. Lemmers et al. [31] described a reduction of $crSO_2$ in preterm infants born before 32 weeks of gestation in association with a hemodynamically significant ductus arteriosus. The ductus arteriosus in preterm infants is thin walled and less muscular compared to those in term born infants, rendering a complete closure immediately after birth less likely [29]. Ductus arteriosus closure is less pronounced in preterm infants compared to term infants during immediate transition especially in case of hypercarbia due to its vasodilatative effect on the ductus arteriosus [32]. This hypothesis is further supported by the fact that the difference between systolic and diastolic blood pressure was more pronounced in preterm infants compared to the term infants in the present study. Therefore, in preterm infants, higher pCO_2 values may be associated with a higher steal phenomenon compared to term, causing a decrease in CBF and oxygen delivery to the brain, ultimately leading to lower $crSO_2$ and higher cFTOE and cTOE.

Limitations

There were limitations in the present study. First, analyzed preterm and term infants showed pCO_2 values within acceptable ranges for the immediate transition period. pCO_2 values outside normal ranges, which are associated with an impaired autoregulation and changes in CBF, might influence cerebral oxygenation, cFTOE, and cTOE more than it was observed in this present study. Second, no measures of CBF and cerebral blood volume were performed, as this study analyzed secondary outcome parameters of observational studies. Direct measures of CBF might have allowed us to understand autoregulation better. Third, we can only assume a possible left-to-right shunt via the ductus arteriosus and foramen ovale especially in preterm infants, as no echocardiography was performed. Fourth, the number of analyzed preterm infants in this present study is quite low and included mainly moderate to late preterm infants, due to the inclusion criterion of no need for respiratory or medical support and the short time period between 14 and 18 min after birth for performing blood gas analysis.

To conclude, we found a significant negative correlation between pCO_2 and $crSO_2$ and a significant positive correlation between pCO_2 and cFTOE and cTOE after immediate postnatal transition in preterm infants. There were no associations observed in term infants at all, except for pCO_2 and pO_2. The present findings suggest that the vasodilatative effect of high pCO_2 levels that would normally result in an increase of cerebral perfusion and oxygen delivery and an increase of $crSO_2$ levels is less pronounced in preterm infants during immediate transition. This vasodilatative effect of pCO_2 is even outweighed by other influencing parameters causing a decrease in $crSO_2$. This might be even more important in compromised extremely preterm infants, especially if pCO_2 values are above or below normal ranges.

Acknowledgments

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Statement of Ethics

The studies analyzed in this post hoc analysis were approved by the Institutional Ethical Review Board of the Medical University of Graz, EC Nos. 19-291 ex 07/08, 23-403 ex 10/11, and 27-465 ex 14/15. Written parental informed consent was obtained before birth and inclusion in each study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.W. and G.P. conceived the research idea and finalized the methods. C.W. and G.P. analyzed the data, and C.W. wrote the first draft. C.W., M.B., B.S., L.M., B.U., and G.P. contributed to data collection, interpretation of the results, drafting, and finalizing the manuscript.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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