The effect of changes in tPCO2 on the cerebral fractional tissue oxygen extraction – as measured by near-infrared spectroscopy - in neonates during the first days of life

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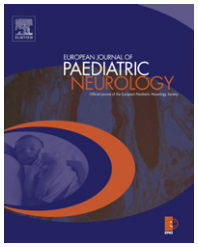

Original article

The effect of changes in $tPCO_2$ on the fractional tissue oxygen extraction – as measured by near-infrared spectroscopy – in neonates during the first days of life

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ABSTRACT

The cerebral fractional oxygen extraction (FOE) reflects the balance between cerebral oxygen delivery (OD) and consumption (VO_2). PCO_2 affects the cerebral blood flow (CBF): hypocapnia decreases CBF and OD and increases FOE. We recently showed that the fractional tissue oxygen extraction (FTOE) reflects FOE and hypothesized that a decrease in $tPCO_2$ increases FTOE. In this study we looked at the effect of changes in $tPCO_2$ on FTOE.
We analysed 23 measurements in 13 neonates with birth weight below 1500 g and need for intensive care. Exclusion criteria were congenital malformations or cerebral complications. The tissue oxygenation index (TOI), $tPCO_2$, mean arterial blood pressure (MABP), heart rate (HR) and peripheral oxygen saturation (SaO_2) were continuously recorded for 4 h during the first days of life and FTOE was calculated.
Over the whole group we found a significant negative ($r = -0.227$) correlation between $tPCO_2$ and FTOE and a significant positive ($r = 0.258$) correlation between $tPCO_2$ and TOI. After correction for MABP these correlations remained significant.
Over the whole group we found a significant positive correlation between $tPCO_2$ and TOI and a significant negative correlation between $tPCO_2$ and FTOE, which remained significant after correction for MABP. This implies that $tPCO_2$ influences the cerebral oxygenation independently of MABP. We therefore believe that for the interpretation of cerebral oxygenation in mechanically ventilated neonates during the first days of life continuous measurements of $tPCO_2$ are needed. Moreover we suggest FTOE to become a continuous parameter in the clinical setting for the non-invasive measurement of the neonatal brain oxygenation.

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1. Introduction

Periventricular leukomalacia is an important cause of morbidity in very low birth weight infants and has been associated with hypocapnia during the first days of life.[1] Hypocapnia can cause neurological damage by diminished oxygen delivery through decreased cerebral perfusion.[2] It is therefore important to analyse cerebral neonatal

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oxygenation and metabolism, taking into account changes in $tPCO_2$.

The cerebral fractional oxygen extraction (FOE) reflects the balance between cerebral oxygen delivery (OD) and consumption (VO_2)[3–5] and thus reflects the cerebral oxygenation. FOE is influenced by $tPCO_2$ through its effect on the cerebral blood flow (CBF): hypocapnia causes vasoconstriction whereas CBF and also OD decrease and FOE increases. Hypercapnia on the other hand causes vasodilatation. The resulting increase in CBF and OD causes FOE to decline.[2,6]

Spatially resolved spectroscopy (SRS) uses near-infrared spectroscopy (NIRS) and allows the continuous and non-invasive measurement of the balance between oxygenated (HbO_2) and deoxygenated (HbR) cerebral haemoglobin. This technique yields an absolute value expressed as the tissue oxygenation index ($TOI = k\ HbO_2/(kHbO_2 + kHbR)$) which reflects the cerebral oxygenation.[7–10]

Using TOI as measure of the cerebral venous saturation and SaO_2 as a measure of the cerebral arterial saturation, the cerebral fractional tissue oxygen extraction (FTOE) can be calculated as (SaO_2-TOI)/SaO_2. In a recent study we showed a good correlation between FTOE and the cerebral FOE.[8]

In this study, with NIRS we wanted to investigate the effect of spontaneous changes in $tPCO_2$ on the cerebral tissue oxygenation- in particular FTOE- in neonates with respiratory support, during their first days of life.

2. Materials and methods

2.1. *Patient population*

Between June 2005 and November 2006, prematurely born infants at the Neonatal Intensive Care Unit (NICU) of the University Hospital of Leuven with a postmenstrual age up to 34 weeks, a birth weight less than 1500 g, an arterial line and in need of intensive care (ventilation or CPAP) were included in the study. Infants with congenital malformations or cerebral complications such as intraventricular haemorrhage (IVH $>$ 1) or periventricular leukomalacia (PVL) at the start of the study were excluded. A cranial ultrasound was done in all infants before the start of the measurements. Informed parental consent was required for participation in the study. The Medical Ethical Committee of the Universital Hospital approved the study.

2.2. *Monitoring cerebral tissue oxygenation and extraction*

We used the NIRO 300 (NIRO 300, Hamamatsu®, Hamamatsu City, Japan) to measure the cerebral haemodynamics and oxygenation. This device uses near-infrared spectroscopy (NIRS) to measure changes in oxygenated haemoglobin (ΔHbO_2), reduced haemoglobin (ΔHbR) and total haemoglobin (ΔHbT) of the brain. Near-infrared light at four different wavelengths, i.e. 775, 810, 850 and 910 nm is sent into tissue to calculate proportional concentration of the two chromophores (HbR and HbO_2).

With spatially resolved spectroscopy (SRS) the TOI of the brain can be measured. Near-infrared light is sent into tissue and becomes attenuated due to scatter loss and absorption loss. If the distance between the light source and the sensor is large enough (more than 3 cm), the isotropy of scatter distribution becomes so homogeneous that the scatter loss gets the same at the three sensors. TOI can be calculated according to the diffusion equation as followed:

$$\frac{k\ HbO_2}{k\ HbO_2 + k\ HbR} = TOI(\%)$$

Where k is the constant scattering distribution.

Because with SRS absolute values are provided, this technique is less sensitive for movement artefacts and continuous measurements are possible.

To investigate the balance between oxygen delivery and consumption we calculated the fractional tissue oxygen extraction (FTOE), which reflects FOE[8] and can be derived from SaO_2 and TOI:

$$\frac{SaO_2 - TOI}{SaO_2} = FTOE$$

The NIRO 300 optodes were placed at the right frontoparietal side of the infant with a 4 cm interoptode distance and a differential pathlength factor of 1.39. The data were recorded in an analogue way with a sampling frequency of 6 Hz by the data acquisition system Codas (Dataq Instruments®, USA).

The Ethics Commission of the University Hospitals Leuven approved the use of near-infrared spectroscopy.

2.3. *Study design*

All physiological and cerebral parameters were continuously recorded for at least 4 h during the first days of life. Heart rate (HR) and peripheral oxygen saturation (SaO_2) were monitored using pulse oximetry on the right or left limb (Novametrix Medical Systems®). The mean arterial blood pressure (MABP) was recorded with a Hewlett Packard 78353A® monitor and transcutaneous PCO_2 with the TINA™ Radiometer™. These physiological parameters were recorded in an analogous way with a sampling frequency of 100 Hz by the data acquisition system Codas (Dataq Instruments, Akron, OH, USA®) and stored in a PC.

Simultaneously the cerebral parameters (HbO_2, HbR, HbT and TOI) were continuously recorded using the NIRO 300.

Blood gasses were taken and $PaCO_2$ was assessed, according to the decision of the attending neonatologist.

During the measurements the infants were observed by the nurses at our NICU. Only those periods during which the infant was quite or asleep and during which every parameter (MABP, $tPCO_2$ and TOI) was reliably recorded were analysed. In contrast periods during which the measurements were not reliable due to movement artefacts or calibration of the $tPCO_2$ monitor, were excluded for further analysis.

2.4. *Data analysis*

To investigate the ratio between oxygen delivery and consumption, we calculated the FTOE as (SaO_2-TOI)/SaO_2.

Data are summarised as median values over 5 min.

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2.5. Statistics

A Spearman test was used to asses the correlations between $tPCO_2$ and TOI and FTOE, and between MABP and TOI and FTOE, for each measurement individually as well as over the whole group. The partial correlation was used to correct for MABP. A p-value <0.05 was considered significant.

The Wilcoxon test was used to look at differences in correlations between $tPCO_2$ or MABP and TOI and FTOE between the different postnatal days.

3. Results

Twenty-three measurements in 13 neonates (subject A till M) were studied. Five measurements were performed on day 0, 7 on day 1, 6 on day 2 and 5 on day 3 of life.

The mean artefact-free recording time of each measurement was 3 h and approximately 29 values (2 h and 25 min) per recording could be used for further analysis.

The gestational age ranges from 24 to 34 weeks (median 27) and birth weight from 700 to 1310 (median 950) g. The clinical data of the study population are listed in Table 1.

Saturation values remained stable and ranged between 81.4 and 98.6% with a median value of 93.5%.

At random time points blood was withdrawn and $PaCO_2$ was measured. With the Spearman test we found a significant correlation (spearman correlation (SC) = 0.650) between these $PaCO_2$ values and the $tPCO_2$ values we continuously measured.

Table 1 – The study population: clinical data

Infant	Gestational age (weeks)	Birth weight (g)	Postnatal age at day of measurement (days)
A	26	1020	A_0, A_1
B	34	1110	B_0, B_1
C	27	980	C_0, C_1
D	27	730	D_0, D_1
E	27	1310	E_0, E_1
F	31	735	F_1, F_2, F_3
G	24	700	G_1, G_2
H	27	840	H_2
I	27	860	I_2, I_3
J	26	950	J_2
K	28	1135	K_2, K_3
L	25	750	L_3
M	29	1220	M_3
MEDIAN	27	950	
MIN	24	700	
MAX	34	1310	

The gestational age (weeks) and birth weight (g) for each infant individually as well as the minimum, median and maximum values over the whole population are outlined.
In the fourth column the postnatal day(s) at which the measurement(s) are performed are provided: '$_0$' stands for 'measurement performed on day 0' (within the first 24 h of life); '$_1$' stands for 'measurement performed on day 1', etc.

The minimum, maximum and median values of the physiological variables MABP and $tPCO_2$ and the cerebral parameters TOI and FTOE for each measurement individually as well as over the whole group are listed in Table 2.

The median values of $tPCO_2$ and MABP from day 0 up to day 3 are plotted in Figs. 1 and 2, respectively.

All neonates were mechanically ventilated.

Over the different days and for the whole group we saw a significant positive correlation (SC=0.258) between tPCO2 and TOI (Fig. 3) and a significant negative correlation (SC = −0.227) between $tPCO_2$ and FTOE (Fig. 4). After correction for MABP, we still found a significant positive correlation between $tPCO_2$ and TOI (partial correlation (PC) = 0.219; $p = 0.000$) and a significant negative correlation between $tPCO_2$ and FTOE (PC = − 0.108; $p = 0.011$).

Over the whole group we found no significant correlation between MABP and TOI (SC = − 0.025) or MABP and FTOE (SC = 0.061). Moreover between the different postnatal days we found no significant difference in correlations between MABP and TOI or FTOE, or between $tPCO_2$ and TOI or FTOE, neither after correction for MABP.

4. Discussion

Our experiments show a positive correlation between $tPCO_2$ and TOI and a negative correlation between $tPCO_2$ and FTOE, also after correction for MABP, in neonates during the first days of life. These findings confirm earlier studies of our group and others and stress the impact of PCO_2 as a physiological variable on the neonatal cerebral perfusion and oxygenation.

Prematurely born infants are extremely vulnerable to disturbances in the brain circulation which may lead to complications: periventricular leukomalacia is the result of changes in CBF and/or OD and has been associated with hypocarbia.[1,11–13]

The effect of CO_2 on the CBF was first described by Kety et al. who found an increase in CBF wit an increase in inspired CO_2.[14] A decrease in CO2 on the other hand causes vasoconstriction of the the cerebral circulation with a concomitant decrease in CBF.[15] This is well described in foetal[16] and newborn lambs,[6,17] as well as in piglets[18–22] and human preterm infants[23] using invasive, preliminary techniques. With Doppler flow measurements, additional studies are performed in human adults,[24–27] anaesthetised children[28] and preterm infants.[29–31]

These studies nicely describe the reaction of $PaCO_2$ on CBF but most of them are limited because they are based upon relative values that are obtained after a stepwise or gradual change in however CO_2 levels whereas fewer points are generated and critical points and non-linearities may be missed. The Doppler technique however does allow the continuous measurement of CBF but cannot assess the coupling with cerebral metabolism. Although this is recommended because hypocapnia influences the cerebral oxygenation. A decrease in PCO_2 causes an increase in the anaerobic metabolism by which the cerebral oxygen demand increases.[32] Together with a decrease in CBF and OD,[6,17,33] and a concomitant increase in oxygen demand hypocapnia finally leads to a decrease in the venous oxygen saturation.[14,34] These findings

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Table 2 – The minimum, median and maximum values of the physiological parameters MABP (mmHg) and $tPCO_2$ (mmHg) as well as the cerebral parameters TOI (%) and FTOE for each measurement individually as well as the over the whole study population are outlined

	MABP (mmHg)			$tPCO_2$ (mmHg)			TOI (%)			FTOE		
	MED	MIN	MAX	MED	MIN	MAX	MED	MIN	MAX	MED	MIN	MAX
Individual measurements												
A_0	36.8	27.3	42.2	51.4	38.5	74.3	74.1	68	78.2	0.166	0.11	0.201
B_0	57.3	48.7	62.1	70	62.4	76.4	65.7	63.7	70.4	0.344	0.304	0.37
C_0	40.7	39.2	41.9	84.7	83.8	86.7	61.5	60.4	62.6	0.29	0.284	0.308
D_0	33.8	28.6	39.7	53	40	57.5	76.1	38.9	86.5	0.168	0.11	0.295
E_0	33.2	28.4	40.6	39.5	35.3	41.2	58.9	52.8	67.2	0.373	0.186	0.408
D_1	33.6	28.5	43.2	50.8	37.3	60.7	65.6	59	70.2	0.266	0.235	0.355
E_1	35.4	33.7	41.3	38.1	30.4	43.4	65.4	61	68.5	0.327	0.296	0.361
B_1	57.3	48.7	62.1	70.1	62.4	76.4	65.6	63.7	70.4	0.314	0.27	0.346
C_1	32.3	29.3	39.3	54.2	50.9	65.5	54.6	51.8	56.6	0.417	0.396	0.439
A_1	36.6	34.4	44.6	62.4	44.3	79.9	61.5	52.3	67.3	0.312	0.235	0.375
F_1	40.2	29.7	46.9	50	43.6	53.5	67	65.7	75.2	0.299	0.216	0.312
G_1	28.8	24.2	30.1	64.4	51.6	78.7	56.1	47.2	62.8	0.484	0.242	0.727
H_2	49.9	39.6	51	44.1	39.7	50	70.4	67.3	72.1	0.236	0.222	0.253
F_2	40.4	22.2	41.1	55.8	40.4	62.6	75.2	73.7	80.7	0.162	0.123	0.219
G_2	30.5	17.6	38.2	40.4	30.3	55.1	70.1	66.5	76.5	0.205	0.173	0.227
I_2	32.6	26.9	38.4	54.7	38.7	70.4	54.6	48.9	64.5	0.394	0.294	0.45
J_2	46.4	32.2	48.8	47	32.2	54.8	78.9	58.9	84.1	0.107	0.057	0.315
K_2	37.8	30.3	47.8	63.7	46.3	86.7	65.1	57.2	68.3	0.328	0.291	0.413
L_3	41.5	35.7	45.9	5.3	47.7	58	53.4	52.2	56.9	0.399	0.374	0.426
F_3	46.1	42.4	50.5	44.8	35.3	56.3	66	59.1	67.4	0.3	0.284	0.374
M_3	27.7	26.7	29.9	56.3	54.6	58.9	75.9	72.7	78.3	0.183	0.154	0.219
I_3	29.7	25.7	33.3	55.2	46.5	70.9	71	67.1	76.7	0.251	0.198	0.286
K_3	33.4	29.5	41.5	57.5	49.9	69.2	78.8	70.2	82.7	0.182	0.145	0.235
Study population	35.2	17.6	62.1	52.6	30.4	86.7	66.9	38.9	86.5	0.293	0.057	0.45

encourage the need for continuous measurements of the cerebral perfusion (CBF) as well as the oxygenation (OD and VO_2)[35] in neonatal life.

Near-infrared spectroscopy (NIRS) allows the detection of changes in the cerebral oxygenation and can be used to assess the CBF-CO_2-reactivity within a wide range of arterial carbon dioxide tension.[33,36] With NIRS, an association between changes in CBV and $PaCO_2$ is described[37] and Pryds et al. found an increase in CBF with an increase in $PaCO_2$.[33]

Spatially resolved spectroscopy (SRS) offers an absolute value, the tissue oxygenation index (TOI), and provides a non-invasive tool to study the cerebral tissue oxygenation with physiological changes.[38] It is shown by probe replacement studies that absolute TOI values can differ intra- and interindividually[39], although we experience that if the probe is not repositioned, TOI serves as a good trend parameter for continuous and long-term oxygenation measurements. Several authors described a decrease in cerebral TOI with hypocapnia.[40–42]

The balance between cerebral OD and VO_2 is represented by the FOE. Under most circumstances, cerebral VO_2 is maintained by alterations in OD and thus CBF, rather than

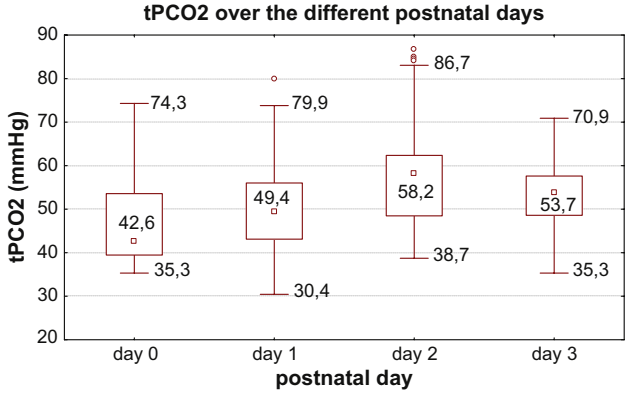

Fig. 1 – The median $tPCO_2$ (mmHg) values for the different postnatal days are plotted. The minimum, median and maximum values are indicated.

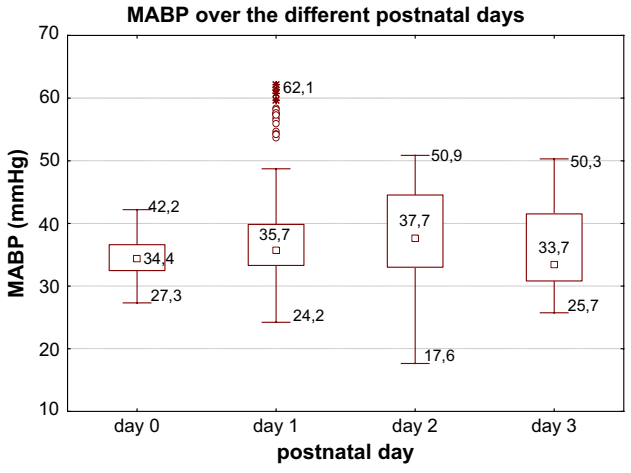

Fig. 2 – The median MABP values for the different postnatal days are plotted. The minimum, median and maximum values are indicated.

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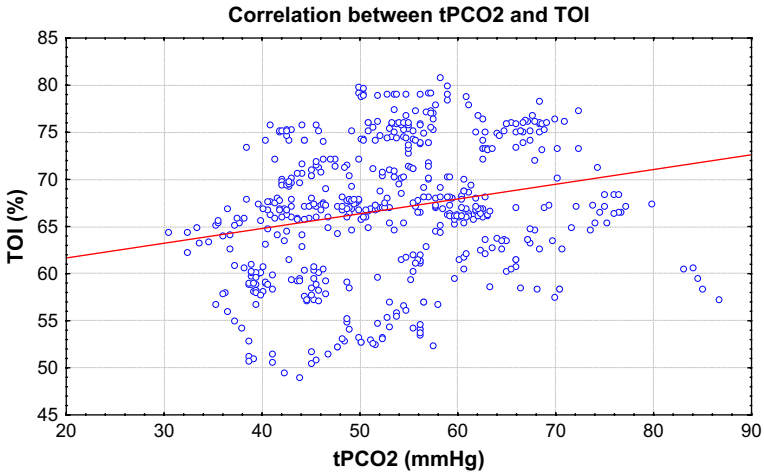

Fig. 3 – The correlation between $tPCO_2$ (mmHg) and TOI (%) is plotted. Over the whole group, a significant positive correlation (spearman correlation = 0.258) is seen.

alterations in FOE.[34,43] Hypocarbia is the one notable exception during which extraction increases dramatically.[43] A negative correlation between cerebral FOE and $PaCO_2$ is found within preterm lambs[17,44] and neonates[4,10] and recently in a study with piglets, a good correlation is described between FOE and FTOE as well as a positive correlation between $PaCO_2$ and TOI and a negative correlation between FTOE and $PaCO_2$.[8] In analogy with these findings, we found a significant positive correlation between $tPCO_2$ and TOI and a significant negative correlation between $tPCO_2$ and FTOE, also after correction for MABP, in human neonates during the first days of life

These changes in oxygenation seen with changes in PCO_2 reflect changes in the CBF. This PCO2–CBF-effect has been studied by Pryds et al. in mechanically ventilated neonates. They found a significant lower PCO_2-CBF-reactivity in these infants at the first day of life[33,45,46] and in addition Wyatt et al. found an increase in the cerebrovascular response (CBVR) with gestational age.[47] Since it is known that: (1) the CBVR to changing $PaCO_2$ is attenuated by hypotension; and that (2) MABP is frequently lower in very premature infants, the reduction in PCO_2-reactivity at younger gestational ages might be secondary to hypotension.[48]

In premature infants, the ability of the CBF to react on changes in PCO_2 is of great interest since low CO_2-reactivity during the first 36 h of life has been associated with poor neurodevelopmental outcome.[49]

In 13 neonates we analyzed the $tPCO_2$-reactivity on the cerebral oxygenation at the first 3 days of life. However, for the different postnatal days, our data failed to reveal any significant difference in correlation between $tPCO_2$ and FTOE, or $tPCO_2$ and TOI. Greisen et al. state that the reduction in PCO_2-reactivity at younger gestational age may be secondary to hypotension.[50] Although in our study population no infants suffered from hypotension. This might explain why significance is not found in our study population although we believe that a greater study population and/or repeated measurements on the different days are needed to confirm these findings.

Besides PCO_2, also MABP affects the CBF in a controlled way[51]: cerebral autoregulation is a protective mechanism assuring a constant CBF over a wide range of MABP values

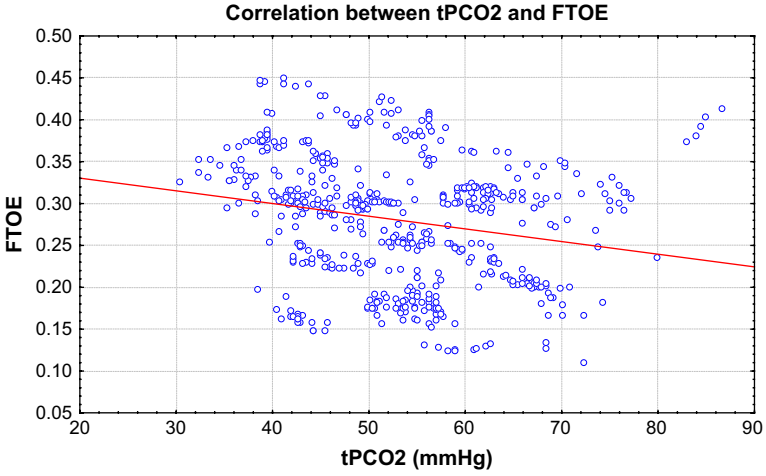

Fig. 4 – The correlation between $tPCO_2$ (mmHg) and FTOE is plotted. Over the whole group, a significant negative correlation (spearman correlation = − 0.227) is seen.

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(i.e. the autoregulatory plateau) the autoregulatory plateau via induction of vasoconstriction and vasodilatation of the resistance capillaries. However MABP values below the lower limit of this plateau cause CBF to decrease whereas MABP values above the upper limit of the autoregulation plateau cause CBF to increase. It has been argumented that cerebral autoregulation may not be fully developed in premature infants and that failure of autoregulation may play a role in the pathogenesis of IVH and PVL.[52,53] In our study over the whole group and over the different days as well as between the different postnatal days, we did not find a significant correlation between MABP and FTOE or TOI suggesting intact autoregulation.[54]

MABP had no effect on the correlations between $tPCO_2$ and TOI or FTOE which implies that $tPCO_2$ influences cerebral oxygenation independently of MABP and that the effect of $tPCO_2$ on the cerebral oxygenation is more pronounced than the effect of MABP. This is in agreement with the statement of Greisen that for the clinical practice in newborns, the relation between pressure and BF is less important than the relation between arterial PCO_2 and BF.[50] Therefore when interpreting the continuous parameters TOI and FTOE, not only MABP but also PCO_2 should be considered as an influencing variable.

5. Conclusion

Our results show a significant negative correlation between $tPCO_2$ and FTOE and a positive correlation between $tPCO_2$ and TOI in mechanically ventilated infants during the first days of life. No significant correlation between MABP and TOI or FTOE over the different days was seen. Therefore we suggest that for the clinical analysis of the cerebral oxygenation not only MABP but also $tPCO_2$ should be measured continuously.

We encourage the use of FTOE as a promising parameter in the clinical setting for the non-invasive, continuous measurement of the brain oxygenation in mechanically ventilated premature infants during the first days of life.

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