Carbon Dioxide Fluctuations Are Associated with Changes in Cerebral Oxygenation and Electrical Activity in Infants Born Preterm

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Objectives To evaluate the effects of acute arterial carbon dioxide partial pressure changes on cerebral oxygenation and electrical activity in infants born preterm.

Study design This retrospective observational study included ventilated infants born preterm with acute fluctuations of continuous end-tidal CO_2 ($etCO_2$) as a surrogate marker for arterial carbon dioxide partial pressure, during the first 72 hours of life. Regional cerebral oxygen saturation and fractional tissue oxygen extraction were monitored with near-infrared spectroscopy. Brain activity was monitored with 2-channel electroencephalography. Spontaneous activity transients (SATs) rate (SATs/minute) and interval between SATs (in seconds) were calculated. Ten-minute periods were selected for analysis: before, during, and after $etCO_2$ fluctuations of ≥5 mm Hg.

Results Thirty-eight patients (mean ± SD gestational age of 29 ± 1.8 weeks) were included, with 60 episodes of $etCO_2$ increase and 70 episodes of $etCO_2$ decrease. During $etCO_2$ increases, brain oxygenation increased (regional cerebral oxygen saturation increased, fractional tissue oxygen extraction decreased; $P < .01$) and electrical activity decreased (SATs/minute decreased, interval between SATs increased; $P < .01$). All measures recovered when $etCO_2$ returned to baseline. During $etCO_2$ decreases, brain oxygenation decreased (regional cerebral oxygen saturation decreased, fractional tissue oxygen extraction decreased; $P < .01$) and brain activity increased (SATs/minute increased, $P < .05$), also with recovery after return of $etCO_2$ to baseline.

Conclusion An acute increase in $etCO_2$ is associated with increased cerebral oxygenation and decreased brain activity, whereas an acute decrease is associated with decreased cerebral oxygenation and slightly increased brain activity. Combining continuous CO_2 monitoring with near-infrared spectroscopy may enable the detection of otherwise undetected fluctuations in arterial carbon dioxide partial pressure that may be harmful to the neonatal brain. *(J Pediatr 2017;187:66-72).*

Although survival rates are increasing, there is a high rate of morbidity in infants born preterm.[1] Cerebral injury acquired in the neonatal period can have a large impact on quality of life. Disturbances in cerebral perfusion and oxygenation can contribute to brain injury in infants born preterm and are associated with impaired neurodevelopmental outcome.[2-4]

Changes in arterial carbon dioxide partial pressure (pCO_2) directly affect cerebral perfusion.[5] Hypercapnia induces vasodilation and hypocapnia induces vasoconstriction of the cerebral arterial blood vessels in newborn infants. To what extent this mechanism is operational in the very preterm infant has not been clarified fully. However, the brain of infants born preterm is susceptible to disturbances in flow owing to relatively immature cerebral vascularization and limited autoregulatory capability.[6]

Abnormal pCO_2 levels have been associated with neuropathology.[7,8] Hypercapnia increases cerebral blood flow with risk of intraventricular hemorrhage (IVH) and periventricular hemorrhagic infarction. Hypocapnia-induced vasoconstriction can lead to ischemic white matter injury. Recent research has shown that fluctuations in CO_2 are also related to severe IVH and increase the risk of neurodevelopmental impairment or death.[7,9]

Fluctuations in pCO_2 are common in ventilated infants and are often caused by respiratory variations. CO_2 fluctuations during continuous end-tidal CO_2 ($etCO_2$) monitoring may not be detected by intermittent arterial pCO_2 analysis. $etCO_2$ shows a good correlation with pCO_2 and can, within certain limits, be monitored continuously in ventilated infants.[10-13]

Our study aimed to analyze the effects of $etCO_2$ fluctuations, as a surrogate for arterial pCO_2, on oxygenation and electrical activity of the brain. Our hypothesis was that acute increases in pCO_2 cause vasodilatation, which in turn might

$etCO_2$	End-tidal carbon dioxide	MABP	Mean arterial blood pressure
EEG	Electroencephalography	NIRS	Near-infrared spectroscopy
FTOE	Fractional tissue oxygen extraction	PDA	Patent ductus arteriosus
GA	Gestational age	$rScO_2$	Regional cerebral oxygen saturation
HR	Heart rate	SaO_2	Arterial oxygen saturation
ISI	InterSATinterval	SAT	Spontaneous activity transient
IVH	Intraventricular hemorrhage		

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increase cerebral oxygenation and reduce electrical brain activity. Acute decreases in pCO_2 result in vasoconstriction and might decrease cerebral oxygenation and increase activity.

Methods

This retrospective, observational study included patients from the neonatal intensive care unit at the Wilhelmina Children's Hospital in Utrecht, The Netherlands. Infants were selected from a cohort of infants born very preterm (<32 weeks of gestation) between October 2009 and January 2016 if they were ventilated with continuous $etCO_2$ monitoring in combination with neuromonitoring during the first 3 days after birth. Obstetric, intrapartum, and neonatal data were collected from hospital patient records. All clinical decisions were made by the attending neonatologist based on current treatment protocols. The target range of pCO_2 was between 40 and 50 mm Hg in ventilated infants. Moderate to severe respiratory distress syndrome was defined by radiographic features and the need for surfactant therapy. Physiological variables were monitored with the Philips patient monitor (IntelliVue MP70, Philips, Best, The Netherlands) and included arterial oxygen saturation (SaO_2) with a pulse oximeter, heart rate (HR), and mean arterial blood pressure (MABP) with an indwelling arterial catheter. Germinal matrix hemorrhages and IVH were diagnosed with cranial ultrasound and graded according to the classification of Papile et al.[14] The diagnosis of a hemodynamically significant patent ductus arteriosus (PDA) was based on clinical symptoms and confirmation by cardiac ultrasound imaging. This study was approved by the Utrecht University Medical Center ethical committee. Parental consent was waived because of the retrospective observational and noninterventional design.

The $etCO_2$ was monitored in exhaled air in intubated infants with the Philips IntelliVue monitor as a surrogate of arterial pCO_2. Acute $etCO_2$ fluctuations were defined as an increase or a decrease of at least 5 mm Hg lasting less than 1 hour, with simultaneous neuromonitoring. The $etCO_2$ signals were manually reviewed and automatically verified to identify acute fluctuations. During each acute $etCO_2$ fluctuation in the first 72 hours after birth, a 10-minute period of stable data was selected. We selected $etCO_2$ increases or decreases of at least 10 minutes and not longer than 1 hour to avoid analyzing chronic hypercapnia or hypocapnia. A 10-minute control period was selected within approximately 1 hour before the change in $etCO_2$ and after the return of $etCO_2$ to baseline.

Neuromonitoring included continuous assessment of cerebral oxygenation and electrical activity during the first 72 hours after birth, which is standard clinical practice in our neonatal intensive care unit for all infants born before 32 weeks of gestation and in all infants with signs of asphyxia, seizures, in case of suspected congenital anomalies, and during neonatal surgery. Regional cerebral oxygen saturation ($rScO_2$) and fractional tissue oxygen extraction (FTOE, calculated as $[SaO_2 - rScO_2]/SaO_2$) were monitored by near-infrared spectroscopy (NIRS) with the INVOS spectrometer (INVOS 5100C, Medtronic, Minneapolis, Minnesota) with a small adult sensor (small adult SomaSensor SAFB-SM, Covidien, Mansfield, Massachusetts).[15] Adult sensors were used because neonatal sensors measure on average 10% higher than the adult sensors, thus, losing variability in the higher regions.[16] Electrical activity was monitored by 2-channel (F3-P3, F4-P4) electroencephalography (EEG) with the BrainZ monitors (Natus, Seattle, Washington). The cross-cerebral (P3-P4) 256-Hz raw EEG signal was used to calculate the spontaneous activity transients (SATs) rate per minute (SATs/minute) and the length of the interval between SATs, the interSATinterval (ISI), in seconds with a nonlinear energy operator in the SignalBase software (SignalBase, University Medical Center Utrecht, The Netherlands).[17] The EEG signal consists of periods of activity alternated with periods of inactivity, corresponding with a discontinuous background activity, where decreased SAT rate and increased ISI reflect a neurodepressant state.[18]

Statistical Analyses

Signal processing was performed with in-house developed software. Artifacts were removed manually. Ten-minute periods of stable monitoring before, during, and after $etCO_2$ fluctuations were analyzed with repeated measures ANOVA with the Greenhouse-Geisser correction if needed, or Friedman's ANOVA in case of nonlinear data. Linear mixed effects model analysis assessed the association between $etCO_2$ and neuromonitoring variables with a random intercept per patient and $etCO_2$ as the independent variable. The effect of $etCO_2$ was analyzed both as a fixed categorical predictor (periods before, during, and after $etCO_2$ fluctuation), as well as a continuous predictor ($etCO_2$ values). With $etCO_2$ as a categorical predictor, the reference category (constant) was the baseline period before the $etCO_2$ fluctuation.

Dependent variables of cerebral oxygenation were $rScO_2$ and FTOE, with an additional fixed effect for PDA. Dependent variables of cerebral functioning measures were SATs per minute and ISI, with additional fixed effect for morphine. Gestational age (GA), postnatal age, and vital measures HR, MABP, and SaO_2 were included in all analyses. $P < .05$ was set to statistical significance. The influence of baseline $etCO_2$ levels was assessed separately. Statistical analyses were performed with IBM SPSS statistics 21 and R (R Core Team, Vienna, Austria, 2012) with the lme4 package.

Results

Clinical characteristics are shown in **Table I**. From the complete cohort of 102 ventilated infants with continuous $etCO_2$ monitoring during the first 72 hours after birth who were born between October 2009 and January 2016, we collected a complete dataset in 38 infants born extremely or very preterm. All infants had NIRS monitoring and 33 patients were monitored with amplitude-integrated EEG. A total of 60 episodes of acute $etCO_2$ increases and 70 episodes of acute $etCO_2$ decreases were identified. Corresponding pCO_2 levels were generally within physiologic limits. During $etCO_2$ increases, $etCO_2$ increased from (mean ± SD) 38.0 ± 5.2 mm Hg to 46.4 ± 5.8 mm Hg and then returned to baseline 38.6 ± 5.2 mm Hg ($P < .001$). During $etCO_2$ decreases, $etCO_2$ changed from