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Is the partial pressure of carbon dioxide in the blood related to the development of retinopathy of prematurity?

Balazs Gellen, Neil McIntosh, Janet R McColm, Brian W Fleck

Abstract
Aims—To determine the role of carbon dioxide in the development of retinopathy of prematurity (ROP).

Methods—This was a retrospective cohort study of 25 consecutive infants admitted to the neonatal unit with continuously recorded physiological data. The daily mean and standard deviation (SD) of transcutaneous carbon dioxide partial pressure (tcPCO₂) was compared between infants who had stage 1 or 2 ROP and stage 3 ROP. The time spent hypocarbic (<3 kPa) and/or hypercarbic (>10 kPa and >12 kPa) was also compared between these groups. Intermittent arterial carbon dioxide tension was also measured and compared with the simultaneous tcPCO₂ data.

Results—There were no significant differences in carbon dioxide variability or time spent hypocarbic and/or hypercarbic between the ROP groups on any day. 86% of transcutaneous values were within 1.5 kPa of the simultaneous arterial value.

Conclusion—TcPCO₂ measurement can be a very useful management technique. However, in this cohort neither variable blood carbon dioxide tension nor duration of hypercarbia or hypocarbia in the first 2 weeks of life was associated with the development or severity of ROP.

Methods
This was a retrospective cohort study of infants who were admitted to the neonatal intensive care unit, Edinburgh, between 1996 and 1998. Inclusion criteria were 14 days of continuous monitored data of transcutaneous carbon dioxide, at least stage 1 ROP, and less than 1001 g birth weight or less than 30 weeks gestation.

Infants were divided into two groups, stage 1 or 2 ROP (ROP1,2 group) and stage 3 ROP (ROP3 group). Stage 3 ROP was defined by the presence of extraretinal neovascularisation. A computerised neonatal cot monitoring system in routine clinical use recorded physiological data including transcutaneous carbon dioxide pressure (tcPCO₂) from Hewlett Packard combined oxygen and carbon dioxide probes and 78344A neonatal monitors. The data were recorded every second and later stored as a 1 minute average of 60 one second data points. After removal of obvious artefact due to probe calibration the mean and standard deviation were calculated for each day of the first 14 days of life. For each period we also noted the number of minutes that the tcPCO₂ was under 3 kPa, was over 10 kPa, and was over 12 kPa. All values were further aggregated over a week or 2 week period to produce a single mean for each statistic for each baby. Arterial carbon dioxide (PCO₂) tension was also measured intermittently by umbilical or peripheral arterial catheter sample and compared with the simultaneous transcutaneous carbon dioxide data.

Retinopathy of prematurity (ROP) is the most commonly acquired retinal disease in premature babies. It is multifactorial, with gestational age and low birth weight being the most powerful predictors of progression to disease. Although originally it was postulated that high arterial oxygen levels were causative, more recently data have shown that fluctuations in arterial blood oxygen tension are more closely related to the development and severity of the disease.

Clinical studies investigating carbon dioxide have shown both hypercarbia and hypocarbia to correlate with retinopathy. Animal studies have established a link to hypercarbia, but difficulty in inducing hypocarbia has made it difficult to resolve these conflicting data.

The aim of this study was to determine whether hypercarbia or hypocarbia or the variability of carbon dioxide in the first 2 weeks of life in extremely preterm infants were associated with the development of ROP. A criticism of the previous clinical studies was that they used intermittent arterial blood gas analysis to associate PCO₂ with pathology, we have analysed continuous transcutaneous carbon dioxide data.
Is the partial pressure of carbon dioxide in the blood related to the development of ROP?

Table 1: Mean (SD) and the variability of tcPCO2 (in kPa) during the first 14 days of life in ROP1,2 and ROP3 group. Significance was defined as p < 0.05 by Student’s t-test.

<table>
<thead>
<tr>
<th>Day</th>
<th>ROP 1,2 tcPCO2 mean</th>
<th>ROP 1,2 tcPCO2 variability</th>
<th>ROP 3 tcPCO2 mean</th>
<th>ROP 3 tcPCO2 variability</th>
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<td>6.2 (0.3)</td>
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<td>0.9 (0.3)</td>
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<tr>
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</table>

Results
Over the 2 year period 50 infants were diagnosed with any stage of ROP and 25 of these babies met the inclusion criteria, the others failing mainly because of a lack of the 2 weeks of continuous monitoring data. Infants enrolled in the study had a mean birth weight of 691 g (530–1245 g) and gestational age 25.2 weeks (range 24–29). Ten were in ROP1,2 group and 15 were in ROP3 group.

There was no statistical difference between mean tcPCO2 values or in the variability of tcPCO2 during the first 14 days of life between the two groups (Table 1). The length of time that the tcPCO2 was under 3 kPa was over 10 kPa, or was over 12 kPa was also not significantly different between ROP1,2 and ROP3 group in either the first or the second week of life.

Figure 1 is a Bland-Altman plot of the intermittently measured PaCO2 versus the simultaneous tcPCO2 data and the differences were not significant; 85.8% of transcutaneous values were within 1.5 kPa of the simultaneous arterial value (1.5 kPa or less difference between tcPCO2 and PaCO2 was accepted in this study as a satisfactory agreement).

Discussion
The present study does not support the view that either increased variability of blood carbon dioxide or a particular duration of hypercarbia or hypocarbia in the first 2 weeks of life is related to the development or severity of ROP.

In this study blood carbon dioxide levels were measured by a continuous transcutaneous monitoring system for 14 days which is in contrast with other studies that have used intermittent blood gas analysis. To ensure that the transcutaneous measurements were accurate they were compared with the simultaneous but intermittently measured arterial carbon dioxide tension. We found that agreement between the methods was usually excellent and the comparison was clinically highly satisfactory.

The transcutaneous measurements resulted in nearly 20 000 data points per baby—each of which in itself was a 1 minute average of 60 one second points. This allowed an objective analysis of the variability of the results, and we plan to use this to investigate the combination of oxygen variability and hypercarbia on the development and severity of ROP.

We wish to acknowledge the assistance given to us by the clinical staff and thank Dr Elizabeth Wood for her role in the pediatric ophthalmological examination. Dr Gellen was funded by a Royal Society/NATO fellowship.