USE OF RESPIRATORY pCO_2 SIGNALS FOR THE ASSESSMENT OF CO_2 REACTIVITY IN NEWBORNS

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Abstract: An increase in arterial pCO_2 levels provokes an increase in cerebral blood flow in normal term babies, but the control system may be impaired in premature or very sick babies. In order to assess the operation of the control system, hypercapnia was provoked by inserting a dead-space in the respiratory circuit of twelve newborns (gestational age 31.2 ± 4.5 weeks and birth weight 1.61 ± 0.95 kg), while simultaneously measuring respiratory pCO_2 (from a side-stream capnograph) and cerebral blood flow velocity (CBFV – from transcranial Doppler ultrasound). There was an increase in respiratory pCO_2 levels in most subjects. CBFV also increased in most cases, but four subjects showed a decrease. Mean end-tidal pCO_2 values were calculated over a one-minute time-window before and after inserting the dead-space. These values were consistently lower than arterial pCO_2 levels, indicating that the capnograph cannot provide robust alternative non-invasive measurements of pCO2 for use in assessing CO_2 reactivity in newborns.

Introduction

Cerebral blood flow (CBF) autoregulation is a sophisticated mechanism which maintains CBF almost constant in spite of changes in arterial blood pressure (ABP). In preterm newborns, failure of autoregulation, has been linked to a number of pathologies, including intraventricular haemorrhage [1].

The partial pressure of carbon dioxide in the arteries ($PaCO_2$) is an important regulator of the cerebral circulation. The neonatal and adult cerebral circulation responds to CO_2 in a similar way, with increased pCO_2 leading to increased blood flow, although the magnitude of the response may be less in neonates [2]. Respiratory control in the neonate, especially in preterm infants, is quite immature when compared to that of adults, making them vulnerable to apnoea and respiratory pauses [3]. Thus many neonates are artificially ventilated, and this makes measuring and modifying their respiratory CO_2 concentration (pCO_2) in order to assess CBF reactivity relatively easy.

The hypothesis that changes in CBF, induced by a rise in $PaCO_2$, might predict subsequent development of periventricular leucomalacia (PVL) in ventilated preterm infants was previously considered [4], and a CO_2 reactivity test applied, with blood gas sampling to assess arterial pCO_2 levels. In equivalent procedures in adults, end-tidal pCO_2 (et-pCO_2) is often used to estimate arterial pCO_2 ($PaCO_2$) [5]. However, the extension of this non-invasive measurement method to newborns under assisted ventilation has not been extensively explored so far. The possibility of measuring $PaCO_2$ non-invasively in the assessment of neonatal CBF reactivity to hypercapnia, would be of potentially great clinical benefit.

For clinical practice the relationship between arterial pCO_2 and blood flow has been considered as even more important than the relation between pressure and blood flow [6]. There are also practical difficulties of measuring the latter, which requires the patient to be catheterized.

In this study CO_2 reactivity is thus tested in term and preterm infants during the first two days of life, considering different parameters from the capnographic signal as indicators of pCO_2 changes. The aim of using capnographic signals is to avoid the need for blood-gas analysis, with is an invasive procedure that requires a small sample of blood, and thus cannot be repeated often, especially in very small pre-term babies. The pCO_2 levels could then be used to estimate 'cerebrovascular reactivity', defined as the ratio of change in CBFV over the change in $PaCO_2$. The objective of this paper is to investigate if these non-invasive measures might provide a robust estimate of arterial pCO_2 with a view to assessing CBFV reactivity to hypercapnia.

Materials and Methods

Twelve ventilated infants (8 preterm and 4 term) with indwelling umbilical catheters from the neonatal critical care units of two Perinatal Hospitals in Rio de Janeiro (Brazil) were studied. Approval from the local ethic committee and informed parental consent were obtained.

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Exclusion criteria consisted of clinical instability, initial $PaCO_2$ higher than 7 kPa [4], cerebral malformation, cardio-vascular abnormalities and lung diseases. Mean gestational age and birth weight were 31.2 ± 4.5 weeks and 1.61 ± 0.95 kg, respectively (mean ± standard deviation). Studies were carried out at 30.5 ± 15 hours after birth.

Each study consisted of the simultaneous recording of arterial blood pressure (ABP), cerebral blood flow velocity (CBFV) and pCO_2. Arterial blood pressure was measured invasively by an indwelling umbilical catheter connected to a blood pressure monitor (Digimax 500, Digicare, Brazil). CBFV recordings were made from the middle cerebral artery using a pulse wave Doppler system (Doppler Frequency 4.0 MHz; hardware and software system developed by the Dept. of Medical Physics, Leicester Royal Infirmary, UK). pCO_2 was measured by a sidestream capnometer (Capnocheck Plus 9004- Sims BCI).

Experimental Protocol. All patients were studied at rest and underwent intermittent mandatory ventilation. In 8 patients, blood samples were collected at the beginning and end of each study for gas analysis. ABP and pCO_2 calibration signals were also recorded. According to the weight of the newborn, a dead-space of 3-12 ml was inserted into the ventilation circuit between the ventilator manifold and the end of the endotracheal tube. Data files were continuously recorded for 12 minutes (an example of part of a recording is shown in Fig. 1). The signals then underwent bidirectional low-pass Butterworth filtering and spurious peaks were removed. Epochs of 60 s duration were selected from before and after dead-space insertion, in order to compare changes in average values of CBFV, ABP and pCO_2 parameters. For the latter, the mean ($mpCO_2$), maximum (et-pCO_2) and minimum pCO_2 ($minpCO_2$) values were found (Fig. 2). Paired t-tests (α = 0.05) were performed for comparisons between values before and after the insertion of the dead -space.

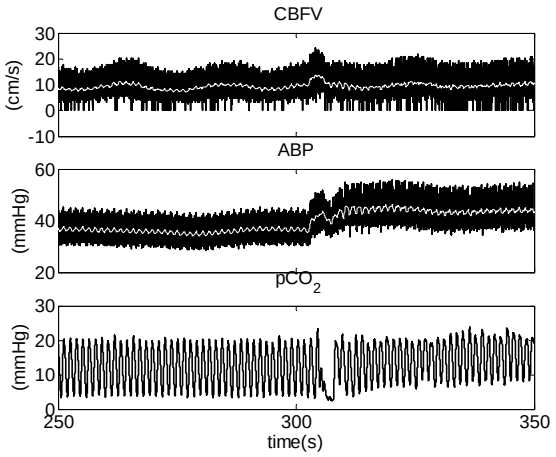

Figure 1: Example of recorded signals during insertion of dead-space (at about 305 s). In this example, the ABP and minimum pCO_2 increased visibly, but CBFV remained relatively unchanged. The white lines over ABP and CBFV signals show the beat-averaged mean signals.

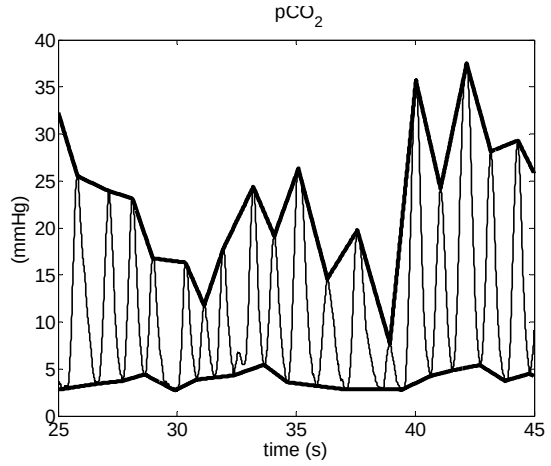

Figure 2: pCO_2 signal with corresponding et-pCO_2 (upper envelope) and minimum pCO_2 signals from a preterm infant under mechanical ventilation.

Results

The pCO_2 signal was unexpectedly variable, and no clear end-tidal plateau was observed in any of the pCO_2 signals recorded, as illustrated in Fig. 2. In adults, such a plateau occurs at the end of expiration, when alveolar air is being exhaled, and its amplitude is taken as reflecting the arterial pCO_2 level.

Increases in minimum, mean and end-tidal pCO_2 were observed in almost all patients after dead-space insertion (Fig. 3). However, the mean baseline (i.e. prior to insertion of the dead-space) et-pCO_2 of 20.8 mmHg was much lower than the mean $PaCO_2$ of 38.1 mmHg measured invasively ($p < 0.0001$). Furthermore, poor correlations were found between arterial measurements and et-pCO_2 ($R= 0.2$, $n= 20$, $p > 0.05$). The increases of arterial pCO_2 and those of the minimum, mean and end-tidal (maximum) pCO_2 were also not significantly correlated. .

An increase in CBFV was found on inserting the dead-space in most subjects, but 4 patients showed a decrease (Fig. 4). Paired t-tests showed non-significant differences in CBFV ($p = 0.26$) and ABP ($p = 0.44$) between the recordings with and without the inserted dead-space. The changes in CBFV and ABP were also not significantly correlated, with the changes in minimum, mean or maximum (end-tidal) pCO_2, nor were the relative changes in CBFV significantly correlated with those in ABP. Multiple and partial correlations of CBFV with ABP and $etCO_2$ were also not significant. The change in each subject's CBFV and et-CO2 is shown in Fig. 5, illustrating the wide inter-

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individual variability. It also shows that in one of the subjects in whom CBFV decreased on insertion of the dead-space, et-CO_2 also fell.

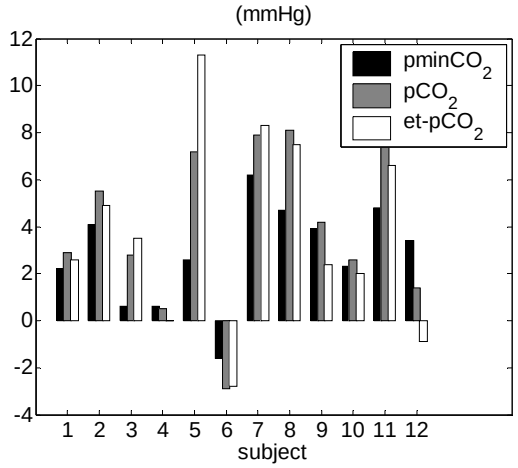

Figure 3. Increase in minimum, mean and end-tidal pCO_2 following dead-space insertion

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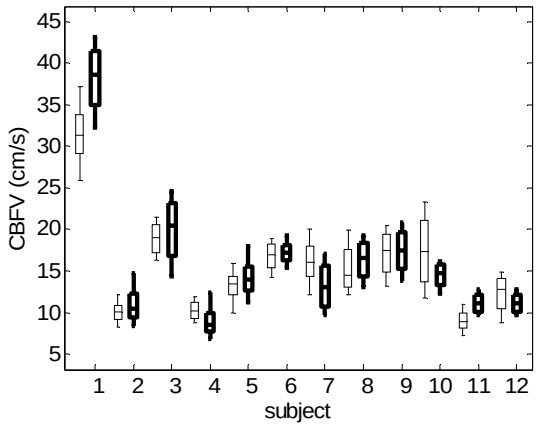

Figure 4. CBFV before and after (bold) insertion of dead-space. The blox-plot shows minimum,and maximum values of CBFV in the one-minute intervals, as well as the median and quartiles.

Discussion

The mean values of end-tidal pCO_2 were considerably lower than those obtained from blood-gas analyses, and below the range of 35–45 mmHg expected in the neonates. In previous work [8] good correlation between end-tidal pCO_2 and arterial pCO_2 in neonates was noted. However, that group used a main-stream capnograph, rather than the side-stream design used in the current paper. The slower response of our system, in which the respiratory gases have to travel down the sample line more than 1 m in length, before being analysed, introduced a delay, and likely loss of high-frequency information. With the relatively fast respiratory rate of neonates, this probably has greater impact than in adults. It is also possible that the insertion of the dead-space increases this delay, further reducing our ability to measure the pCO_2 of alveolar air. Furthermore, in most of the patients there was a contribution from both mechanical and spontaneous ventilation occurring simultaneously, and this probably contributed to the rather irregular pCO_2 signals, which showed great variability between successive end-expiratory values, and very likely biased mean and end-tidal values. It would thus appear that sidestream capnography does not provide a reliable estimate of arterial pCO_2 in these ventilated neonates. Nevertheless, an increase in minimum, maximum and mean pCO_2 values was observed following insertion of dead-space, indicating that the capnograph could detect the expected increase in pCO_2 levels.

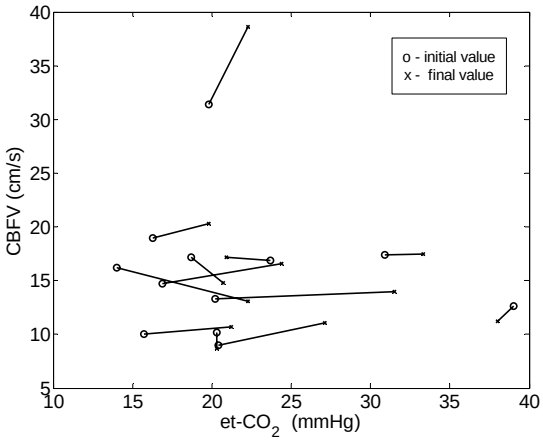

Figure 5. Mean CBFV and et-CO_2 for each of the 12 subjects, before (o) and after (x) insertion of the dead-space.

The increase in CBFV was not found consistently, and in four cases, CBFV dropped on insertion of the dead-space. Previous studies [9] also found that results could be quite variable, and decreases were sometimes observed. There is also some evidence [4] that those in whom blood flow dropped, were at higher risk of developing brain damage. Follow-up studies have not yet been carried out on the current sample.

Due to the lack of a gold-standard method for assessing cerebral blood flow reactivity, we cannot know precisely if patients had impaired control, but the immaturity of some in our sample, and apnoea of others makes this likely [11, 12]. The slightly smaller dead-space we inserted (though comparisons are difficult due to the wide range of weight and size of the neonates investigated) may also have contributed to the less consistent increase in CBFV than observed in previous studies [4, 9]. A small dead-space is desirable and was chosen in order to minimize interfering with the babies. A further factor that makes comparison of our results with those from previous work difficult is the pathologies and prematurity of patients included in the samples. Furthermore, we waited for only 2-5 minutes following the insertion of the dead-space, which may have been too short to observe any consistent CBFV

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changes. However, in adults, most of the increase in CBFV due to hypercapnia occurs within approximately one minute [13], and this is consistent with visual inspection of our data. A shorter time interval between measurements is desirable from practical consideration in a clinical setting, and may also help to reduce changes in the mean values, not associated with the clinical protocol.

As shown in Fig. 1 and Fig. 4, CBFV presents considerable spontaneous variability before and after insertion of the dead-space. Such variability is common, and has indeed been exploited in estimating cerebral autoregulation [10]. Previous studies have also shown that infants breathing out of synchrony with the ventilator show greater CBFV variability than when they are apnoeic or breathing synchronously with the ventilator [6]. From Fig. 4 it may be noted that the increase in CBFV due to the insertion of the dead-space is often within the range of spontaneous variability, making the provoked change less evident.

In summary, the results obtained indicate that the side-stream capnographic pCO_2 recordings do not provide a robust measure of absolute arterial pCO_2 levels, though they do provide an indication of increased pCO_2 after the insertion of the dead-space. The insertion of dead-space into the respiratory circuit provoked an increase in measured pCO_2, but its effect on CBFV was inconsistent. Whether or not this reflects the patients' clinical status or limitations of the protocol requires further investigation.

Acknowledgments

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