

Is ETCO₂ a predictor of PaCO₂ in ventilated neonates on the Neonatal Intensive Care Unit?

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Abstract

Background: A key focus to monitoring ventilator efficacy in critically ill neonates is to avoid the complications caused as a result of hypocarbia and hypercarbia. The current gold standard for monitoring ventilator efficacy is by measuring Arterial Blood Gases (ABGs). However more traditional methods of monitoring include Transcutaneous monitoring and Pulse oximetry (SpO₂). Several reports outline the limitations associated with the accuracy and applicability of these methods.

Aim: To explore the use and contribution of end-tidal carbon dioxide (ETCO₂) monitoring in ventilated neonates on the neonatal intensive care unit.

Search Methods: A comprehensive literature search was conducted by a selection of relevant search terms.

Selection criteria: The selection process was staged to ensure that credible robust evidence was selected against a set of pre-defined inclusion and exclusion criteria. Following this stringent process seven papers were selected.

Main results: Through analysis of the data presented in the seven studies it can be deduced that extension of this method of monitoring to the neonatal group is rendered more complicated by functional issues such as the relatively large dead space, rapid breathing rates with low tidal volumes and ventilation-perfusion mismatch as a result of underlying lung disease. However advances in capnometer technology have allowed for modifications to overcome such limitations. Rozycki et al (1998), Wu et al. (2003), Bhat and Abhishek (2008) and Nangia et al (1997) found a good correlation existed between ETCO₂ and PaCO₂ in patients without underlying lung disease.

Conclusions: Whilst all the studies in this review showed that a correlation exists between ETCO₂ and PaCO₂, this correlation was stronger in the groups with no underlying lung disease. In taking this forward it can be established that whilst ETCO₂ cannot replace the gold standard, it can be used with caution as a valuable trending tool.

Key words: End-tidal carbon dioxide monitoring, capnography, ventilated neonate

Background

Neonates ventilated on the neonatal intensive care unit (NICU) are monitored closely for efficacy of ventilation in an attempt to reduce complications associated with hypoxia, hypocarbia and hypercarbia. This is achieved by a range of monitoring methods such as arterial blood gases (ABGs), pulse oximetry (SpO₂) and transcutaneous (Tc) monitoring. Whilst an ABG remains the gold standard it only provides a snap shot view of ventilator efficacy, and sampling is associated with complications such as

perfusion injuries, air emboli and infections.

Other modes of monitoring have evolved in an attempt to provide continuous non-invasive measurements. These include transcutaneous oxygen/carbon dioxide and SpO₂ monitoring. Whilst these methods of monitoring have become standard practice in many neonatal units they themselves are associated with limitations such as those listed in the table below.

While the more traditional approaches to monitoring ventilation are well established, they have their limitations, and an awareness is required of the advancements in technology to enable one to improve the way in which neonatal ventilation is controlled. One such method is End-tidal carbon dioxide monitoring (ETCO₂). This is a continuous non-invasive method of monitoring that is based on the principle that carbon dioxide (CO₂) will be detected during expiration from a

Table 1: Limitations of Transcutaneous and SpO₂ Monitoring

Transcutaneous Monitoring	Pulse Oximetry
Thermal injury	Information on Oxygenation only
Long Stabilization time	Signal quality
Frequent calibrations required	Pressure sores from probe
Damage to skin with adhesive	Motion artifacts
Slow response time	Electromagnetic interferences

(Carter and Williams 2008)

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correctly placed endotracheal tube (ETT). Initially adopted for anaesthetics, its use to confirm airway patency and lung ventilation has expanded over the last decade to include critical care, emergency medicine, field resuscitation and conscious sedation settings (ASA 2005).

End-tidal CO₂ Monitoring

Capnometers are available as either a side-stream or mainstream sampling device. The use of capnography in neonatal practice is less well documented because of functional limitations including the additional dead space, failure to reach an expiratory plateau during rapid respiratory rates and the technical limitations of ETCO₂ devices to interpret CO₂ in small tidal volume states (Hammer 2006). Recent advances in technology have explored ways in which to overcome such limitations by modifying the capnometer to consider the dynamics of the neonatal lung model with resultant development of a micro-stream device (Colman and Krauss 1999). The clinical application of the device can be interpreted in the capnogram (Fig 1) which represents the concentration of CO₂ in the airway through different phases of the respiratory cycle.

A typical time capnogram can be considered in two parts, i.e. an inspiratory and an expiratory phase. The normal airway CO₂ values are 6-7%, which equates to 45-55mmHg. The CO₂ concentration reflects cardiac output and pulmonary blood flow as the gas is transported by the venous system to the right side of the heart and then pumped to the lungs by the right ventricle (West 2008). When CO₂ diffuses out of the lungs into the exhaled air, a device called the capnometer measures the partial pressure or maximal concentration of CO₂ at the end of exhalation. This represents the ETCO₂ (Fig 1).

Review Process

In undertaking a literature search potential confounding factors were considered. Aim

Several key drivers have led to the development of an evidence based healthcare, requiring one to make use of best evidence to inform practice (Thomson and Dowding 2002).

This review examines the applicability and use of ETCO₂ in ventilated newborn infants on the NICU.

Search Strategy

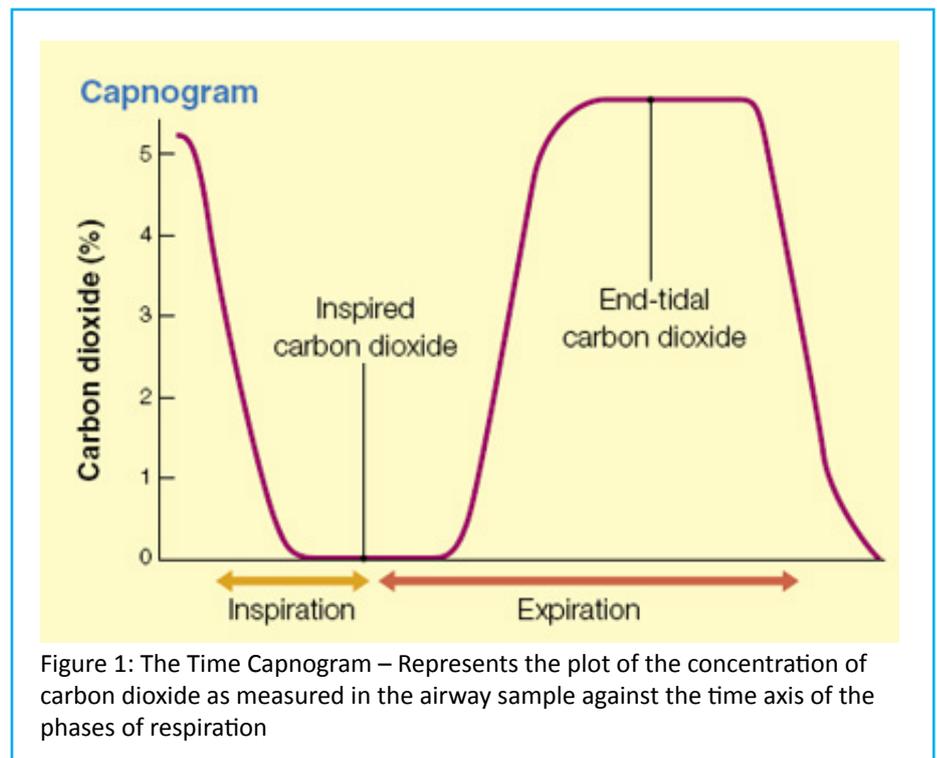


Figure 1: The Time Capnogram – Represents the plot of the concentration of carbon dioxide as measured in the airway sample against the time axis of the phases of respiration

A search strategy was undertaken covering the period May 2009 to February 2010. The initial stages of this literature search involved identifying primary sources, grey literature and expert opinions relating to the use of ETCO₂. The second stage of this search process was formalised by entering search terms namely: “Capnography or End-tidal CO₂ AND ventilated neonates”. The databases accessed included Medline, British Nursing Index, Cumulative Index of Nursing (CINAHL), Pubmed, Cochrane, Journals and Books at Ovid, Health Management Information Consortium (HMIC), The Excerpta Medical Database (EMBASE), Biomed Central, Web of Knowledge, Turning Resource into Knowledge (TRIP), Register for Clinical Trials, Health Information Resources and the Electronic Table of Contents (ZETOC).

Selection Criteria

Studies were included in this review if they were primary research articles published after 1990 studying ventilated neonates on a NICU and focused on the comparison of ETCO₂ measurement with PaCO₂ values.

Studies were excluded if they included older infants, adults or animal studies. To ensure that the search strategy incorporated recent advances in technology, studies prior to 1990 were excluded.

10 studies were identified. To provide a robust review of evidence, studies that mapped well on the hierarchy of evidence were included in this review. Following further evaluation, 3 papers were excluded as they focused around the clinical applications of capnography to the neonatal speciality.

7 studies were identified as eligible for inclusion as they examined the correlation existing between ETCO₂ and PaCO₂. A key strength of these seven studies where that they took place in tertiary centres.

Author	Year	Country	Hierarchy of Evidence	Aim(s) of study	Sample	Methodology	Results
Kugelman, A.				To evaluate a novel method of distal end-tidal CO ₂ (DETCO ₂) by comparison with PaCO ₂ and with a more standard method that measures mainstream end-tidal CO ₂ in intubated infants.	27 infants with median birth weight : 1835 grams	Prospective quantitative study	DETCO ₂ had a good correlation with PaCO ₂ (where n=222, r= 0.72, p<0.001).
Geiger-Aginsky, D., Bader, D., Shoris, I., Riskin, A.	2008		Level 2b		(490g-4790g)	All infants intubated with a double lumen ETT. Neonates had indwelling arterial lines. Infants were connected simultaneously to proximal ETCO ₂ and DETCO ₂ monitors and measurements were compared to PaCO ₂ .	The study further highlighted that DETCO ₂ was a better predictor of PaCO ₂ in neonates with underlying lung pathology.
Israel				Mean gestational age : 32 weeks (24.8-40.8)			
				222 DETCO ₂ - PaCO ₂ pairs			
				212 ETCO ₂ -PaCO ₂ pairs			
Singh, A. S.						Retrospective chart review	Good overall correlation and agreement between ETCO ₂ and PaCO ₂ in surfactant treated, ventilated ELBW babies during the first week of life.
Signal, N.					31 ELBW infants: < 1000g		The Pearsons Correlation Co-efficient was 0.71 with a 95% Confidence Interval.
	2005			To study the correlation and agreement between ETCO ₂ and PaCO ₂ in ventilated extremely low birth weight (ELBW) infants in the first week of life.	21 male and 10 female	All admissions to the NICU	The Bland Altman plot demonstrated a good correlation and the study further demonstrated an intraclass correlation co-efficient of 0.81 (p<0.0001).
Canada			Level 2b		All ventilated	Infants were mechanically ventilated and had indwelling arterial catheters insitu. All infants were connected to a mainstream capnometer. 754 simultaneous ETCO ₂ and PaCO ₂ pairs collected and analysed.	

Wu, Ch., Chou, H.C., Hseih, W.S., Chen, W.K., Huang, P.Y. and Tsao, P.N.	2003	Taiwan	Level 2b	To estimate PaCO ₂ by ET/CO ₂ monitoring in the NICU	61 Patients recruited. 20 term and 41 preterm infants. All patients were ventilated and had indwelling arterial catheters. Main reasons for intubation were either Respiratory Distress Syndrome (RDS) or cardiac disease.	Prospective non randomised single arm study. 130 ET/CO ₂ /PaCO ₂ pairs were analysed from 61 patients.	This study did not show a difference in measurements between preterm or term neonates with underlying lung disease. The researchers showed a positive correlation between ET/CO ₂ and PaCO ₂ . An overall correlation showed 'r'=0.83 where p<0.001. In the term group 'r' = 0.779, p< 0.001 and in the preterm group 'r'= 0.849, p< 0.001. The overall ET/CO ₂ bias (mean +/- SD) was 3.5 +/- 7.1mmHg and a 95% Confidence Interval for the mean of 2.2-4.7.
Rozycki,H.J., Sysyn,G.D., Marshall,M.K., Malloy, R. and Wiswell, T.E.	1998	United States	Level 2b	To determine the accuracy and precision of ET/CO ₂ monitoring in NICU patients	45 Newborn infants. All mechanically ventilated and had indwelling arterial access. A predefined subsample of infants with birthweight < 1000g, < 8 days old and who received surfactant therapy. Patients categorised into SUB group and an ALL group based on the above-mentioned criteria.	Prospective non randomised single arm quantitative study. 411 ET/CO ₂ /PaCO ₂ pairs were analysed from 45 patients. The correlation co-efficient was 0.83, with a 95% Confidence Interval and a 63% accuracy in predicting hypoxia and hypercarbia.	Patients were stratified into two groups. However patients in the SUB groups and ALL groups regardless of gestational age or underlying lung disease demonstrated similar correlation between ET/CO ₂ and PaCO ₂ ('r' = 0.833 and 0.821 respectively with p<0.001).

Haggerty, J.J.,			20 patients (13 in the pulmonary group and 7 in the non pulmonary group).	Prospective nonrandomised pilot study.	Low flow capnography accurately measured alveolar CO ₂ in newborns without pulmonary disease.
Kleinman, M.E.,			Eligible infants were mechanically ventilated and had indwelling arterial catheters in situ.	Capnography was performed through a side port in the proximal ETT.	
Zurakowski, D.,				PeTCO ₂ was measured for one minute pre and post ABG sampling.	The measured PeTCO ₂ - PaCO ₂ gradients were much higher in newborns with underlying pulmonary disease.
Lyons, A.C. and	Level 2b	To evaluate the accuracy of a new low flow side stream capnography and analyse the components of the capnogram in ventilated newborns with and without pulmonary disease.	2 groups were identified: newborns who were receiving ventilation for underlying pulmonary disease and newborns receiving postoperative mechanical ventilation with no underlying pulmonary disease.		
Krauss, B				Newborns in the pulmonary group (n=13) and newborns in the control group (n=7) were matched for birth weight, gestational age and postnatal age.	4 Waveforms were quantified which may be useful differentiating patients with pulmonary disease from those without.
United States	2002			Mean PeTCO ₂ - PaCO ₂ gradients were different between the two groups.	

Table 2: Detail of selected studies

Methodology

Study Design

This review focuses on analysing the relationship between ETCO₂ and PaCO₂ which requires potential confounding factors to be tightly controlled. All studies in this review were therefore correlational and non randomised.

To ensure the validity of results and minimise subjective bias, all patients were evaluated using both the reference standard (ABG) and the test of interest (ETCO₂). Although this method of allocation can potentially lead to systematic bias, the researchers stratified patients into cohorts based on patient characteristics.

Data Collection

The manner in which data is obtained can be susceptible to influences that can alter the results (Polit and Beck 2010). In addition, clearly defined standard protocols for data collection are important in avoiding verification and workup bias (Dawes et al 2005). In all the studies, patients received both ABG and ETCO₂ monitoring, thereby ensuring workup bias was avoided. However, none of the studies discussed a standard protocol of data gathering or analysis. For interventional trials, the accepted analysis is by intention to treat. The equivalent in this study would equate to ensuring that all recorded samples were assessed and that each paired ETCO₂ and PaCO₂ was assessed. Wu et al (2003) refers to measurements being scattered throughout the course of the disease but no further information is provided to allow for reproducibility outside this study. Bhat and Abhishek (2008) and Rozycki et al (1998) stated that ABGs were performed at the discretion of the clinician, whilst Singh and Singhal (2005) have not provided any information on how data was collected. This limitation lends itself to various degrees of errors in measurement and biases. Failure to establish uniformity in data gathering influences the reliability of results. In the study performed by Nangia et al (1997), it is unclear whether the tests were performed independently of each other thereby possibly leading to reviewer bias. However Haggerty et al (2002) provided a basic guide for data collection which correlated with waveform analysis. Wu et al (2002), attempted to minimise inter-

server bias through use of the same respiratory therapist to collect all data.

Data Analysis

Ethics

Rozycki et al (1998), Wu et al (2003) and Haggerty et al (2002) explicitly demonstrated in their studies the application of the ethical principles of research (ICN 2003).

Type of capnometer used

The capnometers used in the clinical setting utilise either side-stream or mainstream sampling. Kirpalani et al (1991) showed that side-stream sampling underestimates PaCO₂ due to the relatively low tidal volumes and rapid breathing rates in neonates resulting in falsely low ETCO₂ readings. Another disadvantage is the delay between sampling and measurement of ETCO₂ (Pascucci et al 1989). However McEvedy et al (1990) showed that both mainstream and sidestream technology produced similar results.

For the studies in this review, Rozycki et al (1998), Wu et al (2003), Bhat and Abhishek (2008) and Singh and Singhal (2005) used mainstream sampling, whilst Nangia et al (1997) used side-stream sampling and Haggerty et al (2002) used micro-stream sampling. However Kugelman et al (2008) aimed to demonstrate that distal ETCO₂ (DETCO₂) was a better predictor of PaCO₂ than mainstream ETCO₂. The use of different methods of ETCO₂ monitoring used across the various studies allowed for a comparison to be made between the different types of capnography.

Reliability and accuracy of the capnometer

Reliability refers to the accuracy and consistency of the information obtained (Polit and Beck 2010). One method of quantifying this would be through proper calibration and application of the capnometer to the breathing circuit. In addition, assessment of sensitivity and specificity will strengthen the reliability of the capnometer allowing the end user to interpret these findings with a degree of confidence.

Rozycki et al (1998), Wu et al (2003), Bhat and Abhishek (2008), Nangia et al (1997) and Singh and Singhal (2005) reported

that capnometers were calibrated as per manufacturer's recommendations. Kugelman et al (2008) and Haggerty et al (2002) did not report any control for calibration of these monitors. All studies in this review used the 'gold standard' (ABG) as a reference interval. The researchers further validated the studies by allowing for upper and lower thresholds for CO₂ concentrations to be determined, providing reference ranges for hypocarbia and hypercarbia.

Patient population characteristics

Singh and Singhal (2005), Kugelman et al (2008), Bhat and Abhishek (2008), Haggerty et al (2002) and Rozycki et al (1998) demonstrated a good degree of homogeneity about gestational age, postconceptional age, birth weight, gender, diagnosis and management strategies. In the study conducted by Wu et al (2003), it is established that the researchers did not provide information about baseline characteristics of the patients recruited into the study. Nangia et al (1997) demonstrated a good degree of generalisability by dividing the group into 3 cohorts.

Confounding Factors

The researchers had to demonstrate tight control of confounding factors for both ETCO₂ and PaCO₂ measurements so that the relationship between these could be understood, thereby eliminating any factors that may obscure the relationship and contribute to type 1 and type 2 errors (Polit and Beck 2010). In order to assess for confounding factors, Rozycki et al (1998) established 2 groups based on the difference between PaCO₂ and ETCO₂ where the difference of $< \pm 5$ mmHg was defined as a low bias group and a difference of $> \pm 5$ mmHg was defined as a high bias group. Similarly Singh and Singhal (2005), Kugelman et al (2008), Wu et al (2003) and Bhat and Abhishek (2008) demonstrated an assessment of confounding factors by assessing for high and low bias groups.

Results

An important feature of clinical trials is that they should be comparative. All studies in this review used a control group of patients without co-existing lung disease, i.e. non pulmonary group. The aim of this review was to determine whether ETCO₂

is a good predictor of PaCO₂. One such method of quantifying this relationship would be to examine the relationship between these two variables. All the researchers, with the exception of Haggerty et al (2002) demonstrated this relationship using correlation coefficients. Haggerty et al used the Pearson's Correlation. In a study conducted by Wu et al (2003) of 60 neonates, the researchers observed a correlation in both term infants (44 samples, $r = 0.78$, $p < 0.001$) and preterm infants (86 samples, $r = 0.85$, $p < 0.001$). Similarly, Rozycki et al (1998) in a study of 45 newborns demonstrated a good correlation between ETCO₂ and PaCO₂ in ventilated neonates including preterm infants, showing correlation coefficients of $r' = 0.833$ and 0.821 respectively with a 95% CI for the biases and $p < 0.001$. In the study conducted by Bhat and Abhishek (2008), the researchers were able to show a correlation and agreement between ETCO₂ and PaCO₂ by demonstrating a correlation coefficient of $r' = 0.73$, with a CI of 95%, where $p < 0.001$. Although a good correlation was demonstrated, the correlation between ETCO₂ and PaCO₂ was greater in the group who were ventilated for sepsis, asphyxia, and apnoea versus those ventilated for Hyaline Membrane Disease or Meconium Aspiration Syndrome. A similar finding was demonstrated in all studies. This leads to the conclusion that conditions with parenchymal lung pathology produce a lower correlation.

Singh and Singhal (2005) conducted a retrospective chart review of extremely low birth weight infants (ELBW) of 754 paired samples using simple linear regression. The researchers reported an intraclass correlation of 0.81.

Bhat and Abhishek (2008) and Haggerty et al (2002), demonstrated a higher gradient between ETCO₂ and PaCO₂ when comparing infants ventilated for pulmonary disease to those ventilated for non pulmonary conditions. Similarly Nangia et al (1997) studied 152 samples in preterm infants <32 weeks gestational age and reported a correlation of 0.55 in the HMD group. This finding conforms to the theory that ETCO₂ poorly predicts PaCO₂ in ventilated neonates with lung disease (Watkins and Weindling 1987) and would be consistent with the disease pattern of these babies i.e. atelectasis with consequent ventilation-perfusion mismatch.

Kugelman et al (2008) found that DETCO₂ was a reliable predictor of PaCO₂ where $r' = 0.72$ with a p value < 0.001 , and mainstream ETCO₂ was a poor predictor of PaCO₂ with $r' = 0.21$ and a p value of < 0.005 .

All the reviewed studies strengthened the outputs of their studies by using a control non pulmonary group. In all these studies, patients in the non pulmonary group showed a better correlation between ETCO₂ and PaCO₂.

Discussion

From conducting this review it can be deduced that limitations exist when applying ETCO₂ monitoring to ventilated neonates. Advances in technology have allowed modification of capnometers to address the challenges posed by the neonatal physiology. This is supported by a study done by Hopper et al in a rabbit model. Here researchers were able to show that inducing lung injury with meconium instillation reduced the correlation between ETCO₂ and PaCO₂ from 0.94 to 0.80 and raised the bias.

A common finding in the studies in this review was that in neonates with underlying lung disease ETCO₂ poorly correlated with PaCO₂. In looking at this group further it was concluded that the patients were predominantly preterm with surfactant deficient lung disease. Surfactant is necessary for lung alveoli to overcome surface tension and remain open. Without adequate surfactant, the shearing forces exerted trying to open alveoli by either the infant's own inspiratory effort or by a mechanical ventilator can induce lung damage. The deficiency in surfactant decreases lung compliance and functional residual capacity resulting in an increased physiological dead space leading to ventilation/perfusion mismatch and poor tidal volumes. This pathological picture may explain why ETCO₂ poorly correlates with PaCO₂ in neonates with underlying lung disease. The studies under review showed that preterm infants who received surfactant therapy showed an improved correlation between ETCO₂ and PaCO₂.

This fits with the theory that following surfactant administration, surface tension is reduced, more alveoli are recruited, and tidal volumes improve thereby reducing ventilation-perfusion mismatch.

In analysing the data presented, it has become clear that whilst ETCO₂ monitoring cannot replace the gold standard of measuring PaCO₂ it can provide useful information if used as a trending tool. This is further supported by Rozycki et al (1998), Wu et al (2003), Bhat and Abhishek (2008) and Nangia et al (1997) who found a good correlation exists between ETCO₂ and PaCO₂ in patients without underlying lung disease. Whilst the researchers were able to demonstrate a good degree of transferability and generalisability through appropriate methods of sampling and methodology, the data was further validated by statistical analysis relevant to this type of study.

In the research presented by Haggerty et al (2002), Singh and Singhal (2005) and Kugelman et al (2008), although the researchers were able to demonstrate a good correlation between ETCO₂ and PaCO₂, inconsistencies lie in the way in which data was collected and communicated. Singh and Singhal (2005) limited the study to extremely low birth weight infants making the findings less transferable, thus making it difficult to extend comparison to infants outside this cohort. Whilst Haggerty et al (2002) demonstrated a good degree of agreement by evaluating the use of the capnometer across two groups, the researchers did not provide any confidence limits or intervals and a correlational relationship between ETCO₂ and PaCO₂ was not established.

Summary

Pulse oximetry and transcutaneous monitoring have been accepted methods of monitoring in the NICU for decades. Interpretation of SpO₂ is a representation of oxygenation only and can be flawed by limitations such as signal to noise ratio induced as a result of poor perfusion and motion artefact. Whilst technologic and engineering advances have addressed these known shortcomings, no definitive solution has been derived to date to ensure an accurate SpO₂ reading for any patient under any circumstances. Whilst SpO₂ monitoring provides valuable data regarding oxygenation its contribution to monitoring ventilation efficacy is limited as it provides no data about CO₂ or metabolic balance that is otherwise obtained from arterial blood gas measurement.

Transcutaneous monitoring represents a simple non invasive technique for contin-

uous monitoring of O₂ and CO₂. Accuracy of this method of monitoring is limited by factors such as thermal injury, skin maturity, long stabilisation times and the need for frequent calibrations and site rotation.

Whilst it can be appreciated that advances in technology have allowed the capnometer to be more applicable to the neonatal population, it cannot replace the gold standard of ABG monitoring. ABGs not only provide valuable data measuring efficacy of ventilation but can also provide a range of valuable data such as electrolytes, blood glucose, lactate etc.

All the studies in this review have explored the correlational relationship between ETCO₂ and PaCO₂. It has become clear that the accuracy of ETCO₂ in predicting PaCO₂ in ventilated newborn infants is limited by various components specific to neonatal pulmonary physiology and the presence or absence of co-existing parenchymal lung disease. However, by accepting and understanding its limitations, capnometry is easily applied and does provide continuous trending data that can rapidly alert clinicians to significant changes in PaCO₂ that may require prompt respiratory assessment. Further advances in capnometer design e.g. micro-stream sampling, will necessitate further evaluation of this modality in clinical practice anticipating that the current performance will be improved upon. The ability to continuously display ETCO₂ can therefore potentially provide a valuable adjunct to our monitoring and assist in optimising the management of the ventilated newborn infant on the neonatal unit.

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