REVIEW ARTICLE

Non-invasive carbon dioxide monitoring in neonates: methods, benefits, and pitfalls

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Wide fluctuations in partial pressure of carbon dioxide ($PaCO_2$) can potentially be associated with neurological and lung injury in neonates. Blood gas measurement is the gold standard for assessing gas exchange but is intermittent, invasive, and contributes to iatrogenic blood loss. Non-invasive carbon dioxide (CO_2) monitoring has become ubiquitous in anesthesia and critical care and is being increasingly used in neonates. Two common methods of non-invasive CO_2 monitoring are end-tidal and transcutaneous. A colorimetric CO_2 detector (a modified end-tidal CO_2 detector) is recommended by the International Liaison Committee on Resuscitation (ILCOR) and the American Academy of Pediatrics to confirm endotracheal tube placement. Continuous CO_2 monitoring is helpful in trending $PaCO_2$ in critically ill neonates on respiratory support and can potentially lead to early detection and minimization of fluctuations in $PaCO_2$. This review includes a description of the various types of CO_2 monitoring and their applications, benefits, and limitations in neonates.

Journal of Perinatology (2021) 41:2580–2589; https://doi.org/10.1038/s41372-021-01134-2

INTRODUCTION

Arterial blood gas (ABG) measurement is the gold standard assessment of gas exchange. With the advent of pulse oximetry, continuous, non-invasive assessment of oxygenation is common practice and has been evaluated in multiple randomized controlled trials in preterm neonates [1, 2]. Non-invasive assessment of ventilation can be performed by end-tidal ($EtCO_2$) or transcutaneous (TCOM) monitoring of carbon dioxide (CO_2). Fluctuations in CO_2 lead to changes in cerebral and pulmonary blood flow and are associated with brain injury [3, 4] and severe intraventricular hemorrhage (IVH) in preterm infants [5] highlighting the importance of continuous monitoring. This article gives a brief overview of the history, methods, benefits, and pitfalls of both types of non-invasive CO_2 monitoring.

History of non-invasive carbon dioxide monitoring

The CO_2 in exhaled gas is an indicator of changes in CO_2 production in the tissues, delivery to the lungs by the circulatory system, and elimination by the lungs. The term "capnography" is used to describe continuous graphic recording (capnogram) of the CO_2 concentration in respiratory gases [6] and can be plotted against time (time capnogram) or volume (volumetric capnogram) of gas. The instantaneous measurement and display of the CO_2 concentration are referred to as capnometry. Its early use dates back to World War II when it was utilized to monitor CO_2 concentrations inside submarines [7].

Capnography was first illustrated by John Scott Haldane in the early 20th century when he built a gas analyzer [8]. A sample of gas at constant temperature and pressure would pass through a series of absorbents, and the concentration of CO_2 could be analyzed based on the reduction in the volume of gas. Photoacoustic detection of sound generated by the pressure change resulting from infrared (IR) light passing through a gas sample [9] and the effect of ultraviolet and visible light on the rotational and vibrational energy of molecules that absorb it [10, 11] was also used to determine the concentration of CO_2. Many decades after the first described CO_2 monitor [12], Holland was the first country to adopt non-invasive CO_2 monitoring during anesthesia in the year 1978 [13, 14]. Shortly thereafter, it was introduced in the United States and became the gold standard in anesthesiology by the 1990s despite the lack of randomized controlled trials [15]. Since the advent of non-invasive CO_2 monitoring for clinical use, several improvisations have resulted in smaller, simpler, and lower-cost versions of exhaled CO_2 detectors/ monitors.

Severinghaus in 1960 reported monitoring of CO_2 and O_2 during anesthesia using various methods including blood gas sampling, $EtCO_2$ monitoring, and "tissue" monitoring [16, 17]. Subsequently, he described transcutaneous monitoring by heating the skin to "arterialize" the sample [18–20]. The latest transcutaneous CO_2 monitors are based on the same principles.

Physiology of carbon dioxide monitoring

Blood perfusing the pulmonary capillary bed is briefly exposed to the alveolar gas. During this short transit in healthy individuals, the PCO_2 decreases from ~46 mmHg in the pulmonary arteriole to 40 mm Hg in the pulmonary venule by equilibrating with alveolar CO_2 (P_ACO_2) [21, 22]. There is a high alveolar-to-atmospheric (atm) PCO_2 gradient of approximately 40 mmHg ($P_{atm}CO_2$ is 0.3 mm Hg since CO_2 constitutes only 0.04% of the atmospheric air). Hence, PCO_2 is recorded as 0–1 mmHg during inspiration in the time capnogram (phase 0, Fig. 1). The exhaled CO_2 is measured by

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Received: 26 March 2021 Revised: 25 May 2021 Accepted: 9 June 2021
Published online: 19 June 2021

infrared spectroscopy (IR spectroscopy) as CO_2 absorbs and emits IR light in a distinct wavelength (4.26 µm).

The 4 phases noted in the CO_2 tracing include the following (Fig. 1):

Phase I: During exhalation, gas from the dead space containing minimal CO_2 is expired initially [23].

Phase II: Subsequently, there is a dramatic increase in the exhaled CO_2 concentration (phase II), which then reaches a peak.

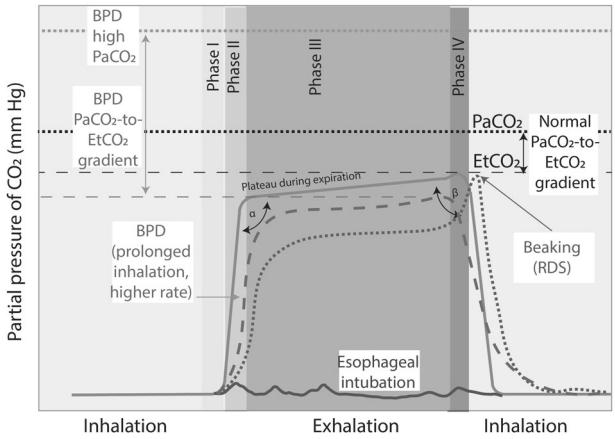

Fig. 1 Time capnogram in which end-tidal CO_2 ($EtCO_2$) is traced against time. Phase I represents the gas from the anatomical and apparatus dead space and hence is CO_2-free. Phase II has a rapid S-shaped upswing (mixing of alveolar gas with the dead space gas). Phase III or the alveolar plateau represents exhaled gas that is rich in CO_2 from the alveoli. Variation in the ventilation/ perfusion (V/Q) status of the alveoli can result in phase III being an extension of phase II. Phase IV or beaking is noted with respiratory distress syndrome (RDS) due to collapse and exhalation of alveolar gas. The change in the waveform in RDS, bronchopulmonary dysplasia (BPD), and esophageal intubation are also shown. The capnogram in BPD shows an exaggerated $PaCO_2$–$EtCO_2$ gradient in BPD. $PaCO_2$ arterial partial pressure of carbon dioxide. *Copyright Satyan Lakshminrusimha*.

Phase III: The CO_2 concentration ultimately plateaus when all the exhaled gas originates from the alveoli. The initial part of phase III is a plateau due to the constant amount of CO_2 being emptied from the alveoli. The alveoli with lower ventilation/ perfusion (V/Q) ratios and longer time constant (i.e., more time to blow out CO_2) contribute to the latter part of phase III, causing a slight upward slope of the plateau phase (also called phase IV).

Phase IV: A terminal blip or upward slope (phase IV) may be observed at the end of phase III due to delayed emptying of the alveoli with a lesser quantity of exhaled air with higher CO_2 concentration. Beaking of phase IV is more common in lungs with poor compliance as in respiratory distress syndrome (RDS) (Fig. 1) [24].

Substantial variation in the V/Q status of the alveoli can result in phase III being an extension of phase II (the slope of the plateau is increased and the α angle between phase II and III is altered from the usual angle of 100°) [24]. The maximum value of PCO_2 at the end of the breath is known as $EtCO_2$. The CO_2 then quickly drops to zero at the end of phase III/IV, due to low levels of CO_2 in the inspired gas. The difference between the $PaCO_2$ and $EtCO_2$ is a marker of physiological dead space, with a difference of 5 mm Hg due to the mixing of alveolar CO_2 with the gas in the dead space without any CO_2 [25]. This difference is increased in the presence of lung disease such as bronchopulmonary dysplasia (BPD) [26].

Types of non-invasive carbon dioxide monitoring

Physical method (waveform capnography). Infrared (IR) spectrography evaluates the absorption of IR rays at a specific wavelength (4.26 µm) by CO_2 [27]. Hence, the quantity of CO_2 in respiratory gases can be measured by comparing the measured absorbance with that of a known standard and expressed as PCO_2 in mmHg.

1. *Endotracheal/End tidal CO_2 ($EtCO_2$) monitoring*: the capnograph sensor is connected to the endotracheal tube (ETT) and allows measurement and recording of $EtCO_2$. These are further classified based on the location of the sensor (Table 1 and Fig. 2):

(a) *Main-stream sensor capnometer* (Fig. 2): The adaptor housing the sensor is connected as an attachment in between the

Table 1. Summary of the advantages and disadvantages of currently used methods of carbon dioxide monitoring in neonates.

Type of CO_2 monitoring	Advantages	Disadvantages
Mainstream $EtCO_2$	Rapid response time, especially helpful in sick neonates in respiratory distress Non-invasive Continuous monitoring is feasible	Physiological dead space and air leakage around the ETT leads to underestimation of PCO_2 Can be inconvenient and adds weight and dead space, which may cause auto-triggering of ventilators. Not reliable in infants with severe lung disease and V/Q mismatch. Cannot be used with non-invasive ventilation in spontaneously breathing infants and with high-frequency ventilation.
Sidestream $EtCO_2$	Easier to use, more convenient with less weight added to the ET tube. Exhaled gas sampled before entry into breathing circuit, thus reducing dilution with dead space gas.	Can be affected by secretions and blockage of the sampling tube. 1–4 second delay in CO_2 reading and capnogram; hence not useful in small tidal volume and fast respiratory rate
Transcutaneous CO_2 ($TcPCO_2$)	Decreases the need for frequent and repeated arterial blood gases. Better correlation with $PaCO_2$ during transport in ventilated infants. Helpful in following the trend in PCO_2 Can be used with high-frequency ventilators and non-invasive ventilation	Inaccurate in the setting of improper placement, entrapped air bubbles, error in the equipment, or in calibration. The stabilization time of ~20 minutes prior to reading the $TcCO_2$. Not reliable in infants with impaired perfusion, acidosis, edema, or vasoconstrictor medications. Risk of burns in the skin; the need for periodical change in its position.
Colorimetric CO_2 detector (CCDD)	Rapid ascertainment of ETT placement, especially in the delivery room during resuscitation.	False-negative in the setting of poor lung perfusion from low cardiac output, pulmonary hypoplasia, low tidal volumes, and air leak (Fig. 6).

$PaCO_2$ arterial partial pressure of carbon dioxide, *$EtCO_2$* end-tidal CO_2, *$TcPCO_2$* transcutaneous CO_2, *CO_2* carbon dioxide, *V/Q* ventilation/ perfusion ratio, *CCDD* colorimetric carbon dioxide detector.

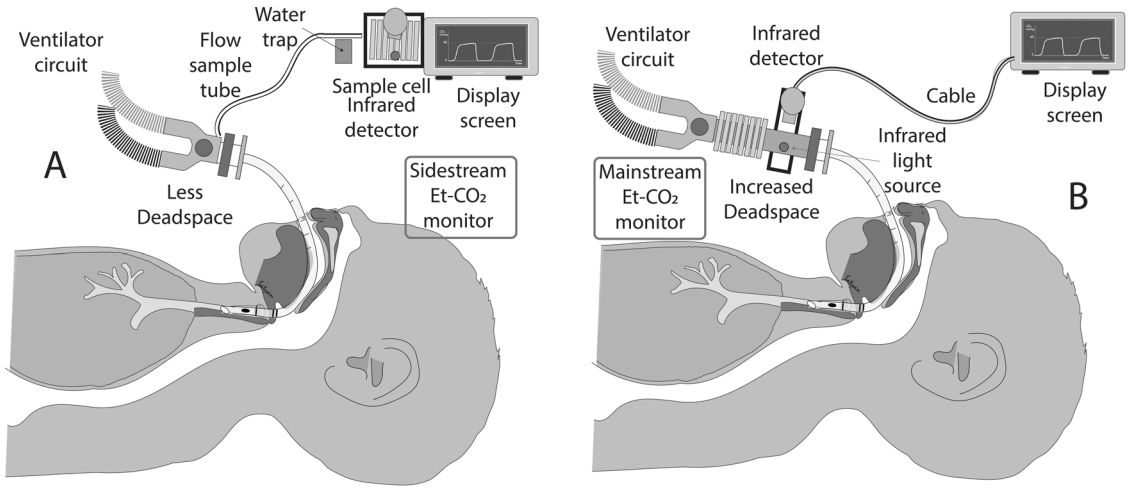

Fig. 2 Types of $EtCO_2$ monitoring. An illustration of sidestream (**A**) and mainstream (**B**) non-invasive CO_2 monitoring. The difference in dead space and sampling method is shown. $EtCO_2$ end-tidal carbon dioxide. *Copyright Satyan Lakshminrusimha*.

ETT and the ventilator circuit. Measurement of PCO_2 is made rapidly across the airway and may underestimate the alveolar PCO_2 since the device adds to dead space in the circuit and competes for tidal volume, resulting in lower values of $EtCO_2$. They can be used in neonates on conventional ventilation, but not on those receiving non-invasive ventilation or high-frequency ventilation. A novel method of distal $EtCO_2$ monitoring by a double-lumen ETT, as reported by Kugelman et al. had a good correlation with $PaCO_2$ that remained agreeable in severe lung disease compared to mainstream CO_2 monitoring [28].

(b) *Sidestream capnometer*: The sensor is located in the main unit with a small pump that aspirates the patient's gas sample through capillary tubing from the proximal part of the ETT. Respiratory gas is then transported from the sampling tube to the IR measuring device causing a 1–4 s delay in PCO_2 measurement and display. Higher flow conventional sidestream capnography (150–200 ml/min) may cause underestimation of PCO_2 due to lower tidal volumes and higher respiratory rates in neonates [29]. However, microstream/low flow technique (50 ml/min) with a dead space of less than 0.5 ml improves the accuracy of sidestream capnography [30–32]. Sidestream capnography can also be used in infants on non-invasive ventilation and high-frequency ventilation [33].

(2) *Transcutaneous CO_2 monitor* (TCOM, Fig. 3): TCOM uses the principle of arterialization of cutaneous capillaries by application of heat [16]. The sensor consists of a glass pH electrode, a silver chloride reference electrode, a heating element, a temperature element, and an electrolyte reservoir. When the sensor (with a membrane covering the electrodes) is applied to the skin, heat is generated that causes vasodilation of cutaneous capillaries and increases the permeability of the skin to CO_2. CO_2 that diffuses through the membrane reacts with water to form carbonic acid, which then dissociates into hydrogen and bicarbonate ions. This results in a change in pH that causes a potential difference between the two electrodes. Based on the linear relationship between pH and Log PCO_2, the PCO_2 measurement ($TcPCO_2$) is obtained and is continuously recorded. The final recording corresponds to the PCO_2 in the cutaneous capillaries which has been shown to correlate well with $PaCO_2$ (between 20 and 74 mmHg), under stable hemodynamic conditions [34].

The immature and thin epidermal layer in premature infants is advantageous for $TcPCO_2$ monitoring. Improved short-term

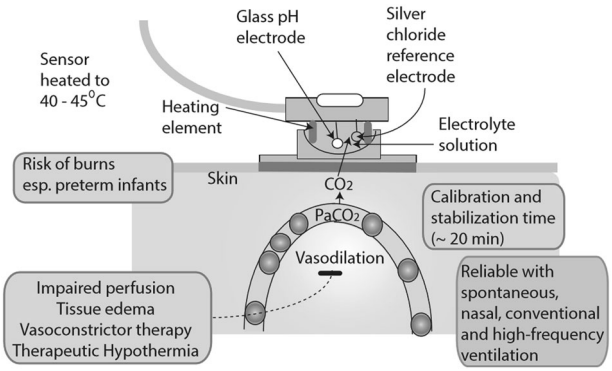

Fig. 3 Trancutaneous CO_2 monitoring. The structure, advantages (green box), and disadvantages (red boxes) of transcutaneous CO_2 ($TcPCO_2$) monitoring in neonates. *Copyright Satyan Lakshminrusimha*.

respiratory outcomes were reported with $TcPCO_2$ monitoring during transport and during high-frequency oscillatory ventilation [35, 36]. Neonatal studies have shown that $TcPCO_2$ correlates better with $PaCO_2$ compared to $EtCO_2$ [37–39]. $TcPCO_2$ readings have been noted to be higher than $PaCO_2$ at higher temperatures owing to two proposed mechanisms: (a) higher solubility of CO_2 at higher temperatures ($TcPCO_2$ 4.5% more than $PaCO_2$) [40], and (b) additional CO_2 being produced from metabolism by the skin cells, and tissue diffusion. Preliminary studies during therapeutic hypothermia indicate that $TcPCO_2$ correlates well with $PaCO_2$ [41].

Relative heating power (RHP, expressed in milliwatts or mW) is the power required to maintain the $TcPCO_2$ sensor at the set temperature [42]. A well-perfused baby will require a higher RHP than a poorly perfused baby to keep the sensor temperature stable in order to provide an accurate estimate of the $PaCO_2$. In critically ill infants, the trend in RHP may be an indicator of the local blood flow. RHP may have potential application in an infant with ductal dependent systemic circulation (such as coarctation of the aorta or hypoplastic left heart syndrome). Any deviations from the RHP-reference that is stored in the system will be displayed as positive or negative RHP values (considering 0 mW as the stored reference). Hence, interpreting $TcPCO_2$ along with the RHP (or local skin perfusion) is prudent.

Chemical method (colorimetric CO_2 detector). The principle underlying the effectiveness of the colorimetric CO_2 detector (CCDD) is the prevalence of low concentration of CO_2 in

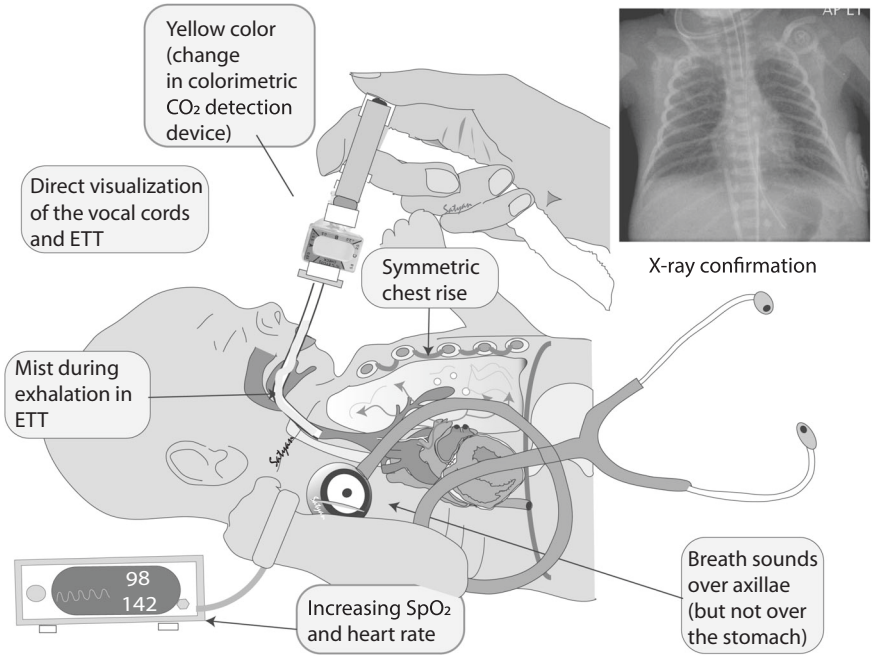

Fig. 4 Confirmation of the endotracheal tube (ETT) placement in the delivery room. Of all these markers, colorimetric CO_2 detection and chest radiograph (X-ray) are helpful in confirming appropriate ETT placement. SpO_2: oxygen saturation. *Copyright Satyan Lakshminrusimha.*

atmospheric air in the esophagus (0.03–0.04%) and high concentration of CO_2 in exhaled gas (4–5%) [43, 44]. A pH-sensitive chemical indicator contained in a plastic apparatus is connected to the gas stream in between the ETT and the ventilator or source of positive pressure ventilation (PPV). Commercially available CCDD at present includes the Pedi-Cap® (Nellcor/Medtronic, Minneapolis MN) and Neo-StatCO_2® (Mercury Medical, Clearwater FL). These semi-quantitative single-use devices display a purple/blue color when CO_2 is low (0.03% to <0.5%) and turn yellow when the concentration approaches 5% [45]. The color changes with inspiration and expiration and from breath to breath, varying based on the CO_2 concentration. Although the Pedi-Cap® is not recommended for infants less than 1000 g, it is widely used to confirm ETT placement in neonates and in-vitro testing showed that it is effective at tidal volumes as small as ~1 ml [46–49]. The NeostatCO_2® device is suitable for infants 0.25–6 kg as per the manufacturer.

Detecting exhaled CO_2 with a CCDD along with a chest radiograph can confirm ETT placement in the respiratory tree; the CCDD is often instantaneously helpful in confirming placement in the delivery room (Fig. 4) [50]. A recent Cochrane review has shown insufficient evidence on the most effective technique to ascertain ETT placement in the delivery room or in the NICU and concluded that randomized trials are needed [51]. CCDD is a valuable adjunct to confirm ETT placement since an anteroposterior chest radiograph may miss esophageal intubation (Fig. 5).

Application in clinical practice in adults

After non-invasive CO_2 monitoring became a standard of care during anesthesia, lawsuits born out of esophageal intubations and unexpected adverse events decreased and the premium to be paid by the anesthesiologists reduced drastically [24]. Widespread implementation of non-invasive CO_2 monitoring resulted in undetected esophageal intubation becoming a "never event" in the United Kingdom [52]. A prospective study from Europe showed a 66-fold higher chance of having an airway catastrophe in ICU when non-invasive CO_2 monitoring was not used [53]. Non-invasive CO_2 monitoring is currently used during procedural sedation, cardiopulmonary resuscitation, in the intensive care unit, during transportation on ventilators, in post-operative care, and in the emergency room. The American Heart Association (AHA) recommends the use of quantitative waveform capnography as a physiological feedback device to monitor the effectiveness of chest compressions (CC) and to detect the return of spontaneous circulation (ROSC, rapid rise in $EtCO_2$ to 35–45 mmHg) [54]. Sanders et al., have shown that $EtCO_2$ positively correlates with coronary perfusion pressure [55]. A prospective matched cohort study on adult in-hospital cardiac arrest (from AHA's Get With The Guidelines-Resuscitation registry) reported a higher likelihood of ROSC when $EtCO_2$ and diastolic blood pressure were monitored [56].

Application in neonates

In normal healthy newborns, the $PaCO_2$ is within the range of 35–45 mm Hg. Cerebral blood flow increases with hypercarbia and decreases with hypocarbia [57–59]. Both hypercarbia (17–30%) and hypocarbia (2.8–4%) are observed commonly among NICU patients [60, 61]. Continuous CO_2 monitoring could potentially decrease adverse outcomes in infants especially vulnerable to fluctuations in cerebral blood flow, such as preterm infants at risk for severe IVH, periventricular leukomalacia (PVL), and BPD, and infants with HIE [59, 62–66]. Managing the ventilator settings and choosing appropriate strategies to ventilate are often gleaned from continuous CO_2 monitoring in addition to bedside clinical evaluation. Intermittent assessments with blood gases come with the risk for periods of abnormally high or low $PaCO_2$ remaining unrecognized and corrective action being delayed.

(1) Use in delivery room during resuscitation.

(a) Mask ventilation: the CCDD serves as a simple tool with immediate feedback to qualify airway patency during mask ventilation in neonates [67–69]. In a single-center retrospective review of video recordings of face mask ventilation with a CCDD, CO_2 detection with CCDD preceded the rise in

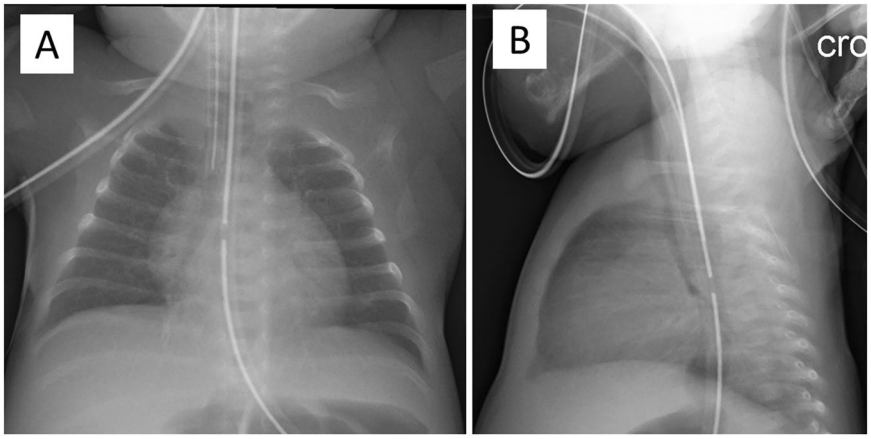

Fig. 5 Importance of capnography in confirmation of endotracheal tube (ETT) position. While chest radiograph is considered confirmatory, an antero-posterior (AP) view can be deceiving (**A**) and a cross-table view might be more accurate in diagnosing esophageal intubation (**B**). Combining an AP view with capnography may be more reliable. *Copyright Satyan Lakshminrusimha*.

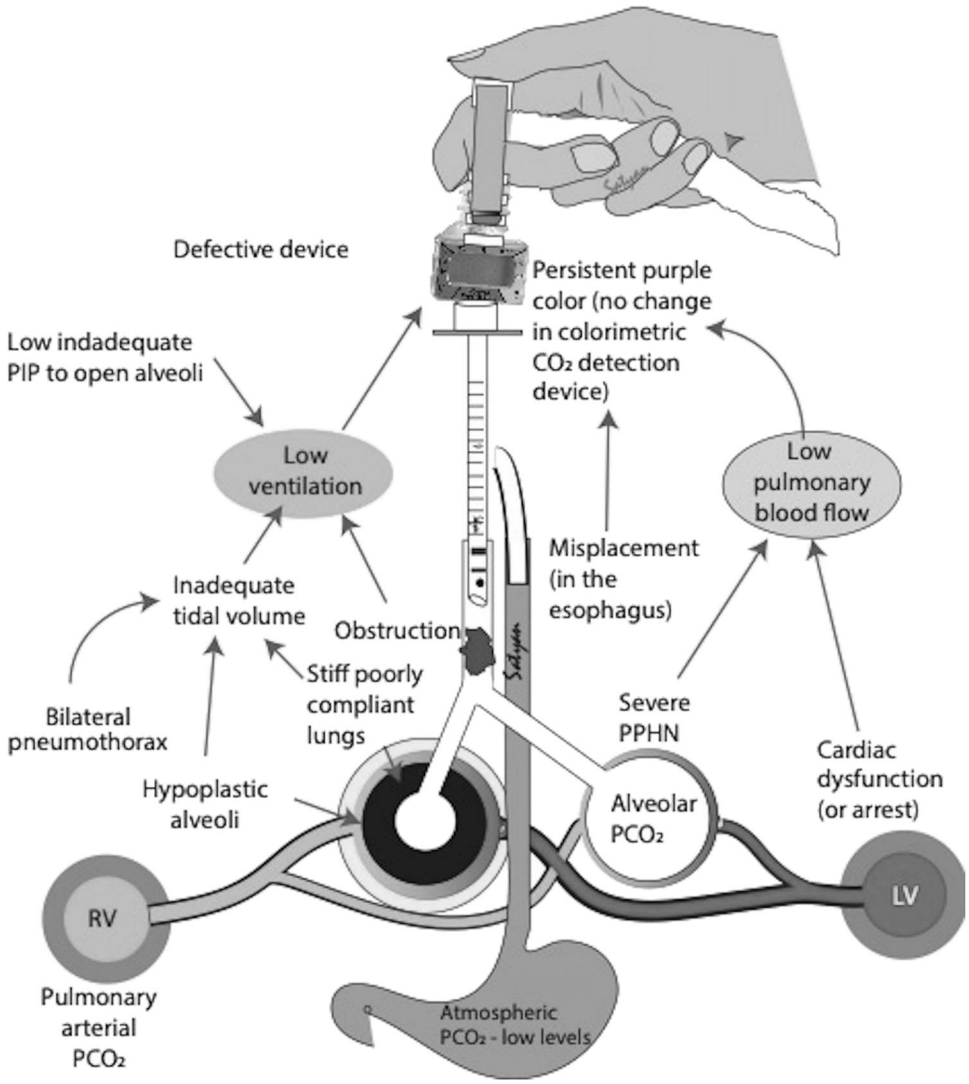

Fig. 6 Causes for persistent purple coloration of colorimetric CO_2 detector in neonates. The most common reason is esophageal intubation. The other causes can be classified into inadequate ventilation and poor alveolar perfusion. PIP peak inflation pressure, PCO_2 partial pressure of carbon dioxide. LV left ventricle, RV right ventricle. *Copyright Satyan Lakshminrusimha*.

heart rate [45]. Clinical observational research in the use of CCDD during PPV with a facemask has advocated their use. Leone et al. described the benefits of CCDD when used with a facemask during PPV in the NICU [46]. In this study, during twenty-one instances of lack of color change on the CO_2 detector, twenty displayed a color change once the head/jaw position was adjusted therefore allowing for easier determination of airway patency [46]. Similarly, van Os et al., showed that a CCDD enables a recognition of airway obstruction in very low birth weight infants during PPV [70]. A literature review by O'Reilly et al. elucidated that facemask leak and obstructions are more often than not unrecognized without the use of CCDD or respiratory function monitors (RM) [71]. However, the use of CCDD during PPV with a facemask has not been advocated in the International Liaison Committee on Resuscitation (ILCOR) guidelines [72] as there is limited data to support their use—therefore it is not routinely used in clinical settings. The overall recommendation for use of CCDD during facemask PPV has been labeled as level C (limited data) [73].

(b) ETT placement: the 2020 AHA and 2016 Neonatal resuscitation Program (NRP) guidelines recommend confirming ETT placement by CCDD or waveform capnography in intubated infants with a perfusing cardiac rhythm (Fig. 5) [74, 75]. CCDD is more accurate as well as quicker in confirming correct ETT placement when compared to clinical assessment [76, 77]. A retrospective analysis conducted by Roberts et al. found that time to recognition of esophageal placement using clinical indicators averaged 97.1 s compared to side-stream capnography (1.6 s) [78]. These findings corroborate the prospective study by Repetto et al. [79] comparing median time to CO_2 detection (9 s) with clinical assessment alone (30 s). Hawkes et al. reviewed studies that evaluated the use of a CCDD in confirming ETT placement and assessed them according to the AHA levels of evidence and grades of recommendation [73]. One such study investigated the Pedi-Cap®'s accuracy in conjunction with respiratory monitoring (RM) on a sample of 35 intubations and found that in 31% (11/35) intubations the Pedi-Cap® failed to change color despite correct ETT placement [80]. Based on current evidence, the recommendation for the use of a CCDD in confirming ETT placement in neonates is level B (moderate-quality evidence). It is possible that CCDD may miss esophageal intubation (false positive) or have a false negative reading despite the appropriate placement of the ETT (Fig. 6) [81].

(c) Chest compressions (CC): Non-invasive CO_2 monitoring as part of RM is of importance in adults during extensive resuscitation including CC to monitor the efficacy of the resuscitative interventions [82, 83], and similar use in neonates as a feedback device is promising. In an ovine model of asphyxial arrest, continuous $EtCO_2$ monitoring predicted adequacy of CC and detection of ROSC [84]. Furthermore, in a large mammalian meconium aspiration model, continuous $EtCO_2$ monitoring limited fluctuation in $PaCO_2$ and cerebral blood flow during and after resuscitation [58]. The use of RM improved the effectiveness of newborn facemask ventilation training in a randomized trial with neonatal manikins [85]. Kong et al. performed a prospective randomized controlled trial comparing PPV adjusted based on clinical assessment alone (blinded to $EtCO_2$) vs. PPV adjusted based on $EtCO_2$ values [86]. Quantitative $EtCO_2$ monitoring in the delivery room did not reduce the proportion of PCO_2 levels outside of a prespecified range in neonates mostly supported with non-invasive ventilation [86]. Hawkes et al. performed $EtCO_2$ monitoring in the delivery room for 39 infants born at 26 5/7 to 31 weeks gestation and did not find any difference between proportions of PCO_2 values within the normocapnia range between infants with and without $EtCO_2$ monitoring [87].

(2) Non-invasive CO_2 monitoring in the NICU.

(a) Minimizing CO_2 fluctuations: Continuous CO_2 monitoring potentially enables us to detect expeditious changes in $PaCO_2$ especially in the first few hours after birth with rapid changes in lung compliance. This allows appropriate and timely adjustments in the ventilator, potentially avoiding prolonged exposure to hypo or hypercapnia, and decrease the duration of invasive ventilation. By avoiding rapid fluctuations in $PaCO_2$ (and hence cerebral blood flow), it may be protective against IVH, and improve long-term outcomes in extremely premature infants and infants with HIE (during and after therapeutic hypothermia) [59, 62–66]. Kugelman et al. performed a randomized multicenter study with $EtCO_2$ visible to the medical team for continuous monitoring in the experimental group and masked in the control group [88]. They observed that IVH and PVL were lower in the monitored group and continuous $EtCO_2$ monitoring improved the control of $PaCO_2$ within a safe range during conventional ventilation in the NICU. A good correlation has been observed between $EtCO_2$ and $PaCO_2$ in ventilated newborns [89]. The discrepancy between $EtCO_2$ and $PaCO_2$ increases with the increasing severity of lung disease and improves after surfactant administration. Nangia et al. observed a significant correlation between $EtCO_2$ and $PaCO_2$ in preterm infants <32 weeks gestation [90]. In another study involving 27 neonates <28 weeks gestation, Aliwalas et al. found only moderate agreement in the first 24 h after birth [91]. A retrospective study in extremely low birth weight (ELBW) infants showed a good correlation between $EtCO_2$ and $PaCO_2$ [92]. To summarize, $EtCO_2$ may be used as an adjunct to clinical assessment and $PaCO_2$ from ABGs, with caution exercised while relying solely on $EtCO_2$ from extremely preterm newborns (and those with severe lung disease) while making ventilatory adjustments. The ILCOR task force has removed the minimum weight of 20 kg for capnography and noted that continuous monitoring has become routine in many settings.

(b) Minimize blood draws: The use of $EtCO_2$ and TCOM can decrease the need for repeated blood gases and iatrogenic blood losses in critically ill or preterm newborns who are prone to anemia. Although not as accurate as blood gases, they are reliable tools in measuring and trending PCO_2 in neonates [89, 93, 94]. CO_2 monitoring may potentially minimize blood draws in stable infants on non-invasive ventilation as well.

(c) Monitoring during transport: $TcPCO_2$ has been shown to be more accurate when compared to $EtCO_2$ for monitoring ventilated neonates during transport [95]. In infants with a perfusing cardiac rhythm, it may be beneficial to monitor $EtCO_2$ either continuously or by frequent intermittent detection of exhaled CO_2 during out-of-hospital, intra-, or inter-hospital transport [74].

(d) Detect accidental extubation: Non-invasive CO_2 monitoring allows the trending of CO_2 among ill neonates in whom the baseline $PaCO_2$ is well established. A sudden change in the waveform (flattening, Fig. 1) or the PCO_2 value may suggest ETT displacement or obstruction, air leak, or an early sign of clinical worsening.

(e) Diagnose hypoventilation: as an aid in the suspicion and diagnosis of central hypoventilation syndrome. Due to reduced respiratory drive (hypoventilation), the infant's $EtCO_2$ and $TcPCO_2$ would climb abruptly to very high values [96].

(f) Surgery (especially abdominal) and post-operative hypoventilation: during abdominal surgeries (such as emergency

Table 2. Gaps in knowledge related to using non-invasive CO_2 monitoring in neonates.

Type of CO_2 monitoring	Existing gaps in knowledge
End-tidal CO_2 monitoring ($EtCO_2$)	Is $EtCO_2$ monitoring feasible during delivery room resuscitation of newborns? Can $EtCO_2$ monitoring be helpful in the delivery room to optimize neonatal ventilation and allow gentle ventilation? Can routine $EtCO_2$ monitoring help in detecting the return of spontaneous circulation in asphyxiated newborns undergoing resuscitation in the delivery room? Should respiratory function monitors with the ability to measure exhaled CO_2, inflation pressure, tidal volume, and air leak around the mask, be routinely used in the delivery room?
Transcutaneous CO_2 monitoring ($TcPCO_2$)	Is it safe, accurate, and reliable in extremely premature and ill neonates? Can $TcPCO_2$ be used to guide clinical decisions in neonates with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia? Is $TcPCO_2$ reliable and in agreement with $PaCO_2$ during surgery/ anesthesia in neonates? Can this technique be used to monitor tissue perfusion and cellular metabolic function? Can relative heating power be used to assess perfusion status?
Colorimetric carbon dioxide detectors (CCDD)	Can routine use with face mask ventilation in the delivery room be beneficial? Can corrective actions for improving the effectiveness of positive pressure ventilation be performed earlier if CCDD is routinely used with facemask ventilation? Can the current pitfalls (inaccuracy due to soiling with epinephrine/ secretions) be overcome? Are CCDD helpful in confirming the position of less invasive surfactant administration (LISA) catheters, and with laryngeal mask airways (LMA)?

$PaCO_2$ arterial partial pressure of carbon dioxide, *$EtCO_2$* end-tidal CO_2, *$TcPCO_2$* transcutaneous CO_2, *CCDD* colorimetric carbon dioxide detector.

exploratory laparotomy for necrotizing enterocolitis, or elective gastroschisis repair), dramatic changes in intraabdominal, and hence intrathoracic pressure may cause a significant effect on ventilation. Prompt recognition by trending $EtCO_2$ or $TcPCO_2$ may allow for expedient ventilatory management. However, on comparing $EtCO_2$ and $PaCO_2$ from 23 prospectively enrolled infants (59 sample sets) during general anesthesia and surgery, mainstream capnography correlated poorly with $PaCO_2$ [97]. Thus, $EtCO_2$ should not be solely relied upon while making ventilatory changes during surgery. Nevertheless, non-invasive CO_2 monitoring (especially $TcPCO_2$) may be helpful in postoperative management to assess the recovery of respiratory drive and alveolar ventilation after anesthesia.

Limitations

There are several gaps that currently exist in our knowledge on neonatal non-invasive CO_2 monitoring (Table 2). Some of the limitations of non-invasive CO_2 monitoring are listed below.

(a) Limitations of $EtCO_2$ monitoring: Despite being a useful adjunct to confirm ETT placement, detection of $PaCO_2$ by waveform capnography has been shown to miss esophageal intubation in 1 in 40 instances [98]. $EtCO_2$ has been used successfully even in ELBW infants. However, wide variation in $EtCO_2$ and poor correlation between $EtCO_2$ and $PaCO_2$ has been noted in critically ill preterm neonates. This is probably secondary to the V/Q mismatch in these newborns with more severe lung disease [31]. $EtCO_2$ measurements are expected to be lower than the $PaCO_2$ due to (i) intrapulmonary shunting with some of the arterial CO_2 bypassing the ventilated alveolar units, (ii) CO_2 being diluted in the conducting airways (anatomical dead space) that do not contribute to CO_2 production and (iii) portions of the lung that are ventilated but not perfused (alveolar dead space, that is increased in worsening lung disease). Inaccurate measurements owing to leakage around uncuffed ETT are not uncommon. The mainstream $EtCO_2$ monitor is bulky and adds to dead space, which may not be insignificant with the lower tidal volume being used to ventilate neonates. In addition, mainstream $EtCO_2$ monitoring cannot be performed in infants on non-invasive ventilation or high-frequency ventilation. Sidestream capnography, on the other hand, may underestimate the $PaCO_2$ due to low tidal volumes and rapid respiratory rates in newborns. High respiratory rates impede the formation of the alveolar plateau phase [99]. Furthermore, phase III of volumetric capnogram was steeper in infants with BPD, likely due to V/Q mismatch, leading to difficulty in differentiating phase II and III [100]. To overcome some of the limitations, sampling from a distal rather than a proximal site, minimizing the length of the tubing, and interpretation with caution for infants breathing at higher respiratory rates (>60 per minute) have been suggested [101]. In addition, distal $EtCO_2$ measured through a double-lumen ETT had a good correlation with $PaCO_2$ even in severe lung disease [28].

(b) Limitations with CCDD (Fig. 6): There are several instances where a CCDD may be falsely negative (purple/blue), including low cardiac output, airway obstruction [48, 76, 77, 80, 102], suboptimal tidal volumes (threshold > 0.72 ml) [48, 49], incomplete exhalation, or an air leak (Fig. 4) [79]. When a fixed pressure is used during PPV, the delivered tidal volume is dependent on the infant's weight, presence of spontaneous breaths (and whether they are synchronized), compliance of the lungs and chest wall, airway resistance, and leak [48, 103]. Conversely, a CCDD may be falsely positive (yellow) with esophageal intubation when expired CO_2 has been forced into the stomach during prior mask ventilation, or during contamination of the colorimetric paper by gastric acid or epinephrine [104]. Bilateral pulmonary hypoplasia (usually due to prolonged oligohydramnios) can potentially limit the volume of exhaled CO_2 leading to false-negative CCDD. Therefore, CCDD readings may be misleading and it is crucial that they are interpreted in conjunction with clinical signs.

(c) Limitations with TCOM: There have been reports of poor correlation with variation in $TcPCO_2$ in preterm and ill neonates [91, 105]. The device should be calibrated using known gas mixtures or the neonate's blood sample and should be corrected for the infant's temperature. The position of sensors should be changed every 4–12 h, depending on the operating temperature of the electrode and the condition of the infant's skin, per the manufacturer's instructions. The $TcPCO_2$ recording may be inaccurate in the

setting of improper placement, entrapped air bubbles, error in the equipment, or in calibration. In order to minimize burns secondary to the high electrode temperature in TCOM, lower electrode temperatures (38–39 °C) have been successfully used with good accuracy after applying a bias correction of 12–15% [106, 107]. However, the main advantages of TCOM are (a) it minimizes the need for repeated blood sampling, (b) allows for trending PCO_2 over a period of time, (c) can be used with any type of ventilator and also in non-ventilated patients, and (d) can be reliably used during transport of ventilated newborns [95].

CONCLUSIONS

In neonates, waveform capnography is widely applied in the NICU for monitoring of ventilated and critically ill term and preterm infants. In addition, both $EtCO_2$ and $TcPCO_2$ provide valuable input in managing infants during the transport of ventilated infants. The use of CCDD has become a standard in the delivery room, as an adjunct to clinical assessment, to ascertain ETT placement prior to confirmation by chest radiograph. Attempts at bridging the existing gaps in our knowledge with regard to neonatal non-invasive CO_2 monitoring can pave the way for its optimal utility in the management of critically ill newborn infants. Furthermore, accurate interpretation of these non-invasive measurements along with astute clinical assessments can expedite evaluation and diagnosis, and lead to swift stabilization and improved outcomes in neonates.

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ACKNOWLEDGEMENTS

The authors would like to thank the funding sources listed below.

AUTHOR CONTRIBUTIONS

DS conceptualized, designed, drafted the initial manuscript, reviewed, and revised the manuscript. LZ, SI, PC, and SL contributed to the concept, reviewed, and revised the manuscript. All the authors have critically revised and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work.

FUNDING INFORMATION

UC Davis Children's Miracle Network, UC Davis Child Health Research Grant and First Tech Federal Union, Canadian Pediatric Society-Neonatal Resuscitation Program Research Grant, National Institutes of Health (NIH)/National Heart Lung and Blood Institute (NHLBI) K12 HL138052, HD072929 and UL1TR001412, and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Compliance with ethical standards

FINANCIAL DISCLOSURE

Dr. Sankaran is supported by UC Davis Children's Miracle Network, UC Davis Child Health Research Grant and First Tech Federal Credit Union, and Neonatal Resuscitation Program Research Grant from the Canadian Pediatric Society. Dr. Chandrasekharan is supported by the National Institutes of Health (NIH)/National Heart Lung and Blood Institute (NHLBI) K12 HL138052 and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) R03HD096510. Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR001412 to the University at Buffalo. Dr. Lakshminrusimha is supported by NICHD (HD072929). The funding agencies did not have any role in the design or submission of this manuscript. This review article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CONFLICT OF INTEREST

The authors declare no competing interests.

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