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**Detection of exhaled carbon dioxide following intubation during resuscitation at
delivery**

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ABSTRACT

Objectives: End tidal carbon dioxide (ETCO₂) monitoring can facilitate identification of successful intubation. The aims of this study were to determine the time to detect ETCO₂ following intubation during resuscitation of infants born prematurely and whether it differed according to maturity at birth or the Apgar scores (as a measure of the infant's condition after birth).

Design: Analysis of recordings of respiratory function monitoring.

Setting: Two tertiary perinatal centres.

Patients: Sixty-four infants, median gestational age 27 (range 23 – 34) weeks.

Interventions: Respiratory function monitoring during resuscitation in the delivery suite.

Main outcome measures: The time following intubation for ETCO₂ levels to be initially detected and to reach 4 mmHg and 15 mmHg.

Results: The median time for initial detection of ETCO₂ following intubation was 3.7 (range 0 – 44) seconds, which was significantly shorter than the median time for ETCO₂ to reach 4mmHg (5.3 (range 0 – 727) seconds) and to reach 15mmHg (8.1 (range 0 – 827) seconds) (both $p < 0.001$). There were significant correlations between the time for ETCO₂ to reach 4mmHg ($r = -0.44$, $p > 0.001$) and 15mmHg ($r = -0.48$, $p < 0.001$) and gestational age, but not with the Apgar scores.

Conclusions: The time for ETCO₂ to be detected following intubation in the delivery suite is variable emphasizing the importance of using clinical indicators to assess correct endotracheal tube position in addition to ETCO₂ monitoring. Capnography is likely to detect ETCO₂ faster than colorimetric devices.

INTRODUCTION

Infants born prematurely commonly require resuscitation in the delivery suite. Seventy-five percent of infants born at less than thirty four weeks of gestation may require some form of positive pressure support, that is facemask ventilation, continuous positive airway pressure (CPAP) or intubation and ventilation.[1] Infants born extremely low birth weight (ELBW, a birth weight of less than 1000 gms) or born very prematurely frequently require intubation in the delivery suite. In one study, in which the aim was to support ELBW infants on nasal CPAP and avoid intubation in the delivery suite, 35% of infants required intubation.[2] A retrospective review reported 40% of ELBW infants required delivery room intubation.[3] In a further study which aimed to stabilize infants born at less than 28 weeks on nasal CPAP, 48% required delivery room intubation [4] and in a UK-based study, 80% of infants born at less than 30 weeks were intubated at delivery.[5] Unfortunately, intubation may not always be successful. The endotracheal tube was incorrectly placed in 17% of attempts in a series of 31 infants with a median gestational age of 28 weeks.[6] Clinical observation is used to assess whether the tube is sited in the trachea, that is, visualization of the endotracheal tube (ETT) passing through the vocal cords. Other determinants of correct placement include chest wall rise with inflations, auscultation of air entry, the appearance of condensation in the tube during expiration and improvements in oxygen saturation, colour and heart rate.[7] Some of these signs, however, are subjective. End tidal carbon dioxide (ETCO₂) monitoring is a more objective method [8-12] and is recommended as the best method to confirm correct endotracheal tube placement by the 2015 International Consensus on Cardiopulmonary Resuscitation.[13] In a study of 100 intubation episodes, 39 of 40 “oesophageal” intubations were correctly identified by ETCO₂ monitoring using capnography and in a mean of 1.6 seconds. In contrast, using clinical indicators oesophageal intubation was only detected by a mean of 97.1 seconds and successful intubation was not detected in five of 60 cases.[8] Furthermore, using a disposable paediatric ETCO₂ detector, oesophageal intubation was detected at a mean of 8.1 seconds compared to a mean of 39.7 seconds using clinical indicators.[9]

ETCO₂ can be detected by capnography, capnometry or colorimetric devices. Capnography and capnometry evaluate ETCO₂ quantitatively. Using capnometry the CO₂ level is displayed as a number, whereas using capnography the level and exhaled CO₂ waveform in real time are displayed. The Pedi-cap® (Medtronic, Minneapolis, Minnesota) is an example of a disposal colorimetric device. It contains a pH sensitive chemical indicator which changes colour in the presence of CO₂. It changes colour from purple to yellow, the colour change commences when the CO₂ level is 4mmHg and is completed when the CO₂ level is 15mmHg. The deadspace is three millilitres and it is recommended for use in infants with a birth weight greater than one kilogram.[14] The Neo-StatCO₂ is an alternative colorimetric device and has a deadspace of one milliliter, it is recommended for use in infants even with a birth weight as low as 250 grams.[15] The colour changes are, however, at higher ETCO₂ levels than with the Pedi-cap®, changing from blue when exposed to air to green in the presence of 7 to 14mmHg CO₂, yellow/green between 15 and 35mmHg CO₂ and yellow when the ETCO₂ level is greater than 35mmHg.

In adult and paediatric populations, it has been recognised that ETCO₂ may be very low or negligible if there is a low or absent cardiac output.[16-18] We have demonstrated that ETCO₂ levels at delivery often remained low before the first active inflation, that is, when an infant makes spontaneous respiratory effort coinciding with a mechanical inflation.[19, 20] This may reflect the lack of vasodilation of the pulmonary vasculature which occurs at the onset of spontaneous breathing,[21] or inadequate lung aeration.[22] Absence of an ETCO₂ signal could be misinterpreted leading to removal of a correctly placed endotracheal tube.[12]

The aim of this study was to determine the timing of the first appearance of CO₂ following intubation using capnography. In addition, we also assessed when the ETCO₂ level reached 4 mm Hg and 15 mm Hg as this would reflect the timings to detection of ETCO₂ using the more sensitive colorimetric device. Furthermore, we assessed whether timing of ETCO₂

detection was related to maturity at birth or the Apgar scores (as a measure of the infant's condition immediately after birth).

METHODS

A retrospective analysis of data collected from respiratory function monitoring during resuscitation in the delivery suite was performed. The monitoring was undertaken at King's College Hospital NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trusts between February 2010 and March 2014. Data from some of the tracers have previously been published.[20] Infants born prior to 34 weeks of gestation and intubated for initial resuscitation in the delivery suite were included in the study. Those with major congenital abnormalities were excluded. Ethical approval was provided by the Outer North London Ethics Committee. The committee required parental consent only for analysis and reporting of the data and this was obtained once the mothers were transferred to the postnatal ward.

Resuscitation protocol

Clinicians attending the deliveries had all completed a Neonatal Life Support course and been trained in the use of the respiratory function monitor. The displayed respiratory function monitoring data was available to the clinical team in real time but, as the monitoring was part of a research study, clinicians were encouraged primarily to follow Neonatal Life Support guidelines. The research team were available to help with the setting up of equipment, but were not involved in clinical decision making.

Positive pressure inflations were generated by a t-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) attached either to the face mask or endotracheal tube. The Neopuff, a continuous flow, pressure-limiting device had a built in manometer, a positive end expiratory pressure (PEEP) valve and a gas flow rate of 5 l/min. The pressure relief valve was set at 30 cm H₂O. The clinicians were advised to follow the UK

recommendations, ie. to use a peak inflation pressure of 20–25 cm H₂O with a PEEP level of 4–5 cm H₂O and to maintain the first five inflations for two to three seconds.[23] The peak inflation pressure was to be increased if chest wall expansion was considered inadequate. All infants were initially resuscitated with an inspired fraction of oxygen (FiO₂) of 0.21. The FiO₂ was subsequently increased if necessary to maintain the oxygen saturation levels between 85 and 92%. The clinical team decided whether to intubate the baby, the criteria used were a heart rate less than sixty beats per minute, poor or absent respiratory effort and/or lack of response to initial facemask resuscitation. They used standard methods to determine whether the ETT was positioned correctly, that is, auscultation of air entry, observation of chest rise and improvement in heart rate and saturations. If the clinical team believed that the ETT was incorrectly placed based on the above criteria, then they removed the ETT.

Monitoring equipment

The respiratory function monitor used was an NM3 respiratory profile monitor (Philips Respironics, Connecticut, USA). The monitor was connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software (3.0.1.4) (Grove Medical, London, UK). The NM3 respiratory profile monitor had a combined pressure, flow and carbon dioxide (CO₂) sensor and this was placed in line between the t-piece and the face mask or endotracheal tube. The NM3 monitor is automatically calibrated for flow, pressure and CO₂ according to the factory stored calibration in the monitor. Oxygen saturation monitoring was also performed, the monitor recorded oxygen saturation and heart rate.

Clinical data

The gestational age at birth and the Apgar scores were determined from the medical records. The number and timing of intubation attempts were identified from the records.

Analysis

The respiratory function monitoring traces were analysed to identify the first successful intubation as indicated by the presence of ETCO₂ and the flow waveform trace; expiratory flow being detected during endotracheal intubation, but not during oesophageal intubation.[24] The starting point was the start of respiratory function monitoring. The analysis was done on the recordings before surfactant was given. The time from the first successful intubation to ETCO₂ levels being detected and ETCO₂ levels being greater than 4 mmHg and 15 mmHg were determined. If ETCO₂ was immediately apparent after intubation and before the initiation of positive pressure ventilation, the time to ETCO₂ was recorded as zero seconds. If the ETT was removed or dislodged before the ETCO₂ thresholds were reached, then the time that the ETT remained in situ was recorded instead of the time for CO₂ rise, as it is unclear how long it would have taken for the CO₂ to be detected had the ETT not been removed or dislodged. Respiratory function monitor recordings were compared to the clinical records of the resuscitations. Episodes of removal of the ETT because the resuscitation team had considered the ETT was misplaced, yet the monitoring demonstrated the endotracheal tube was correctly sited, were noted.

Statistical analysis

Data were assessed for normality using the Shapiro-Wilk test and found not to be normally distributed. Wilcoxon sign rank tests were used to compare differences between the time for any CO₂ to be detected and the time for the CO₂ level to rise above 4 and 15 mHg. The strengths of correlations were assessed using Spearman Rank correlations. Statistical analysis was carried out using IBM SPSS for Windows version 22.

RESULTS

Respiratory function monitoring traces were available from 85 infants, but nine infants had a congenital diaphragmatic hernia and were excluded from analysis. Of the 76 remaining

infants, 64 were intubated during initial resuscitation and form the study population. They had a median gestational age of 27 (range 23 – 34) weeks and birth weight of 905 (range 484 – 2370) grams. Their median Apgar scores were five (range 0-9) at one minute and eight (range 0-10) at five minutes. Fifty infants (78%) had received at least one dose of antenatal steroids and 24 infants (38%) were delivered by caesarean section. Forty-six infants were successfully intubated on the first attempt, eleven on the second and seven on the third attempt.

The median time to successful intubation was 121.5 (range 0-665) seconds. More immature infants were more likely to be successfully intubated sooner ($r=0.273$, $p=0.029$). The time taken for intubation was not significantly related to the time for ETCO_2 to be detected ($r=0.16$, $p=0.22$).

The median time for detection of ETCO_2 following intubation was 3.7 (range 0 – 44) seconds. The median time for ETCO_2 to reach 4mmHg was 5.3 (range 0 – 727) seconds and to reach 15mmHg was 8.1 (range 0 – 827) seconds. The time for any ETCO_2 to be detected was significantly shorter than the times to reach 4mmHg and 15mmHg (both $p<0.001$). In one infant who was reintubated several times, the ETCO_2 was detectable but never rose above 4mmHg during the 34 minutes of recorded resuscitation.

There were no significant correlations between the Apgar score at one minute and the time taken for ETCO_2 to reach 4mmHg ($r=0.18$, $p=0.16$) or 15mmHg ($r=0.15$, $p=0.24$). There were no significant correlations between the Apgar score at five minutes and the time taken for ETCO_2 to reach 4mmHg ($r=0.20$, $p=0.11$) or 15mmHg ($r=0.19$, $p=0.14$). There were negative correlations between gestational age and the time taken for ETCO_2 to reach 4 mmHg ($r=-0.44$, $p<0.001$) or 15 mmHg ($r=-0.48$, $p<0.001$) (Figure 1). There were significant negative correlations between birthweight and the time for ETCO_2 to reach 4mmHg and ($r=-0.35$, $p=0.004$) and 15mmHg ($r=0.371$, $p=0.003$), but there was no significant correlation

between birthweight z-score and the time for ETCO₂ to rise. In 41 infants heart rate data was available. There was no significant correlation between the heart rate at intubation and the time for ETCO₂ to be detected ($r = -0.177$, $p=0.296$) or to rise above 4mmHg ($r= -0.298$, $p=0.073$) or 15mmHg ($r = -0.263$, $p=0.116$).

Of the twelve infants in whom it took more than 30 seconds for the ETCO₂ level to reach 4mmHg, heart rate data are available for seven and oxygen saturation data for four. All but one of the infants were bradycardic between 60 and 85bpm (the other baby had a heart rate between 120 and 140 bpm). Oxygen saturations ranged between 30 and 90%, with no rapid change in oxygen saturations seen after the ETCO₂ rose.

The time taken for ETCO₂ to be detected at all and to rise above the defined thresholds of 4mmHg and 15mmHg was negatively correlated with both the tidal volume ($r=-0.66$, $p<0.001$; $r=-0.54$, $p<0.001$; $r=-0.51$, $p<0.001$) and the compliance level ($r=-0.65$, $p<0.001$; $r=-0.54$, $p<0.001$, $r=-0.51$, $p<0.001$).

There were six intubation attempts where the clinical team had recorded that intubation was unsuccessful, but the endotracheal tube was correctly placed as demonstrated by the detection of ETCO₂.

DISCUSSION

We have demonstrated that, although the median time for ETCO₂ to be detected was short, there was a wide range. Furthermore, there was an inverse relationship between the time to ETCO₂ detection and gestational age, suggesting there may be slower pulmonary vasodilation in very prematurely born infants.

Our results suggest that respiratory function monitoring at delivery might improve recognition of correct endotracheal tube position. In six infants the intubation attempts were recorded as

unsuccessful, but the endotracheal tube was correctly placed as demonstrated by the detection of ETCO_2 . Clinicians, however, must be properly trained in the use of such monitoring at delivery. Indeed, a survey of junior neonatal trainees highlighted that one third would reintubate if ETCO_2 was detected, but there was no chest wall movement and 57% would reintubate if ETCO_2 was not detected.[25] If there is no ETCO_2 detection, but the clinical team felt the endotracheal tube was in the correct place, we would recommend checking the morphology of the flow waves on the respiratory function monitoring if available and ensure there was adequate chest wall rise and the oxygen saturations and the heart rate were rising. Surfactant should be administered once there was certainty the tube was correctly placed.

Despite use of ETCO_2 monitoring being recommended by UK Neonatal Life Support guidelines since 2010 to confirm endotracheal tube placement,[23] it was only used in 9.8% of SCBUs, 19.8% of LNUs and 24.1% of NICUs in a survey carried out in 2012.[26] In a randomized trial two methods of ETCO_2 detection (the disposable PediCap ETCO_2 detector (qualitative) and a microstream side stream capnography device (quantitative)) were compared during face mask ventilation in the delivery room.[27] No significant difference was found in the primary outcome, the presence of normocarbica obtained in the neonatal unit within an hour of birth. There were also no significant differences between the two groups regarding the intubation rate, days of ventilation or bronchopulmonary dysplasia. The authors, therefore, recommended that the use of either form of ETCO_2 monitoring should be considered during newborn resuscitation.[27] Our data, however, demonstrates ETCO_2 is likely to be detected faster by capnography than by a colorimetric device. The presence of ETCO_2 was detected significantly quicker by a capnograph than the time to reach the ETCO_2 level when a colour change would be first observed using a colorimetric device. A further limitation of the colorimetric device is that contamination with gastric fluid, surfactant or medications such as atropine and adrenaline can lead to false positive results.[28] We, therefore, suggest capnography would be more useful than colorimetry.

The time for ETCO₂ to be detected was negatively correlated with the tidal volume, this is consistent with previous research that has demonstrated that after an infant makes a spontaneous respiratory effort, the tidal volume increases.[19] Hence, if there is no change in the inflation pressures, the compliance improves, thus we saw a negative correlation between the time for the ETCO₂ to be detected and the compliance. Following the infant making a spontaneous respiratory effort, the end tidal carbon dioxide level increases [20], which is related to the degree of lung aeration [22].

There are strengths and some limitations to our study. Detailed respiratory function monitoring was analysed, including waveform capnography that allows for detection of very small amounts of ETCO₂. The endotracheal tube was sometimes removed or dislodged before the ETCO₂ rose above our defined thresholds. In such cases, we took the time of extubation or tube dislodgement as the time to ETCO₂ rise as it was not possible to determine how long it may have otherwise taken for ETCO₂ to be detected, particularly if reintubation attempts were unsuccessful or prolonged. This means that the time to ETCO₂ rise and the ranges reported are a 'lowest possible' estimate of the time taken for CO₂ to become detectable. We did not include a Pedicap in series with our ETCO₂ monitoring and hence can only speculate that the CO₂ limits we set would correlate with the colour change on the Pedicap. We did, however, use the CO₂ levels stated by the manufacturer for colour change to occur.

In conclusion, we have demonstrated that in prematurely-born infants intubated in the delivery room, the time taken for ETCO₂ to be detected was very variable. Our results show that monitoring of ETCO₂ levels detected that infants were successfully intubated, but clinical criteria did not. Use of ETCO₂ monitoring should, therefore, be used in conjunction with other clinical signs and monitoring to identify endotracheal tube position.

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Contributor statement: Drs Hunt and Yamada analysed the data. Drs Murthy and Bhat collected the data. Professors Greenough and Milner and Drs Campbell and Fox designed the study. All authors were involved in the production of the manuscript and approved the final version.

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What is already known on this topic

- Detection of end tidal carbon dioxide (ETCO₂) is recommended to detect correct endotracheal tube placement following intubation of newborns.
- The end tidal carbon dioxide level is related to degree of lung aeration.

What this study adds

- There was a wide variation in the time taken for end tidal carbon dioxide to be detected after intubation during resuscitation of prematurely-born infants
- The time for ETCO₂ to reach 4 mmHg was significantly longer than for any ETCO₂ to be detected.
- End tidal carbon dioxide may take longer to rise in babies of lower gestational ages

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FIGURE LEGENDS

Figure 1: Correlation between gestational age and time for carbon dioxide to rise above 4mmHg (left) and 15mmHg (right) (an outlier is excluded from the figures, an infant of 24 weeks gestation in whom the time taken to reach 4 mmHg was 727 seconds and to reach 15 mmHg was 827 seconds).