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A Novel Method of Distal End-Tidal CO_2 Capnography in Intubated Infants: Comparison With Arterial CO_2 and With Proximal Mainstream End-Tidal CO_2

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What's Known on This Subject

Capnography is not commonly used in NICUs because of technical problems and its relative inaccuracy in conditions of ventilation-perfusion mismatch.

What This Study Adds

We showed D_{ETCO_2} measured by a Microstream capnograph via the extra port of a double-lumen ETT to have good correlation and agreement with $Paco_2$, to be reliable in severe lung disease, and to be more accurate than standard mainstream P_{ETCO_2}.

ABSTRACT

OBJECTIVE. The objective of this study was to evaluate a novel method of distal end-tidal CO_2 capnography by comparison with $Paco_2$ and with the more standard method that measures mainstream proximal end-tidal CO_2 in intubated infants.

METHODS. Included in the study were all infants who were ventilated with conventional mechanical ventilation and intubated with a double-lumen endotracheal tube in our NICU during the study period. Data were collected prospectively from 2 capnographs simultaneously and compared with $Paco_2$. Sidestream distal end-tidal CO_2 was measured by a Microstream capnograph via the extra port of a double-lumen endotracheal tube. Mainstream proximal end-tidal CO_2 was measured via capnograph connected to the endotracheal tube.

RESULTS. Twenty-seven infants (median [range] birth-weight: 1835 [490–4790] g; gestational age: 32.5 [24.8–40.8] weeks) participated in the study. We used for analysis 222 and 212 measurements of distal end-tidal CO_2 and proximal end-tidal CO_2, respectively. Distal compared with proximal end-tidal CO_2 had a better correlation with $Paco_2$ and a better agreement with $Paco_2$. The accuracy of distal end-tidal CO_2 decreased, but it remained a useful measure of $Paco_2$ in the high range of $Paco_2$ ($\geq$60 mm Hg) or in conditions of severe lung disease. A subanalysis for infants who weighed $<$1500 g (13 infants, 84 observations) revealed a good correlation and agreement between distal end-tidal CO_2 and $Paco_2$ and poor correlation and agreement for proximal end-tidal CO_2.

CONCLUSIONS. Distal end-tidal CO_2 measured via a double-lumen endotracheal tube was found to have good correlation and agreement with $Paco_2$, remained reliable in conditions of severe lung disease, and was more accurate than the standard mainstream proximal end-tidal CO_2. *Pediatrics* 2008;122:e1219–e1224

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Key Words
end-tidal carbon dioxide, mainstream $ETCO_2$, Microstream technique, preterm infants, sidestream $ETCO_2$

Abbreviations
$ETCO_2$— end-tidal CO_2
ETT— endotracheal tube
D_{ETCO_2}— distal end-tidal CO_2
P_{ETCO_2}—proximal end-tidal CO_2
OI— oxygenation index
$Paco_2$—partial pressure of CO_2 in the alveoli
VLBW—very low birth weight
Pao_2/PAo_2 ratio—arterial to alveolar oxygen tension ratio

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CONTINUOUS NONINVASIVE MONITORING of CO_2 levels in the NICU is important because it may protect infants from the complications of hypocarbia[1,2] and hypercarbia[3,4] and avoid extra blood sampling, which may cause anemia,[5] discomfort, and pain. Capnography, which displays the level and the waveform of CO_2 in exhaled air, provides information on cell metabolism, blood perfusion, and alveolar ventilation.[6]

The use of end-tidal CO_2 ($ETCO_2$) for monitoring and as a tool for verifying endotracheal tube (ETT) position is a common practice in the operating room and in adult ICUs and PICUs.[6] Recently, it was also introduced to NICUs.[7] Capnography is not commonly used in NICUs because of technical problems (eg, leakage around uncuffed ETTs) and its relative inaccuracy in conditions of ventilation-perfusion mismatch.[8,9]

It is possible to measure $ETCO_2$ by mainstream or sidestream capnometry/capnography. Mainstream capnometry was found to be more accurate[10–16]; however, the sampling position used for mainstream capnometry/capnography is connected inline between the proximal ETT and the ventilator circuit. Thus, it adds dead space and competes for tidal volume, and its weight may kink the ETT. When a flow sensor is connected to the ETT, the use of mainstream

capnography is even more cumbersome. Sidestream $ETCO_2$ may have an advantage of possible use in the distal part of the ETT. Distal $ETCO_2$ ($DETCO_2$) may be less susceptible to air leak or mixing of the measured $ETCO_2$ with inhaled air. Furthermore, there is now a new technology, the Microstream technique, that can also improve the accuracy of sidestream $ETCO_2$ in newborns.[9,17]

To take additional advantage of the benefits of distal measurement of $ETCO_2$, we used an innovative technique. Instead of inserting a catheter into the ETT to sample $DETCO_2$, which may partially occlude the airway,[11,18,19] we sampled the distal air via the extra lumen of a double-lumen ETT. This also enabled continuous $ETCO_2$ monitoring.

We hypothesized that $DETCO_2$ as measured by the Microstream technique via a double-lumen ETT would have better or at least comparable correlation and agreement with $PaCO_2$ as the proximal end-tidal CO_2 ($PETCO_2$) measured by mainstream capnography. The aim of our study was to evaluate this novel method of measuring $DETCO_2$ by comparison with $PaCO_2$ and with the more standard method that measures mainstream $PETCO_2$ in intubated infants.

METHODS

Study Design

This prospective study was conducted at Bnai-Zion Medical Center (Haifa, Israel) between April and October 2007. Infants were connected simultaneously to $PETCO_2$ and $DETCO_2$ monitors, and the measurements were compared with $PaCO_2$ drawn for patient care. Measurements of $DETCO_2$ were not used for patients' clinical care. The study was approved by the institutional review board in our center. Parents of all infants signed an informed consent form.

Our primary outcome measure was to evaluate the accuracy and the correlation of Microstream $DETCO_2$ with the gold standard of $PaCO_2$. The secondary outcome measure was to compare these findings with the more standard and commonly used method of mainstream $PETCO_2$.

Study Population

Included in the study were all infants who were ventilated with conventional mechanical ventilation in the NICU during the study period, who were intubated with double-lumen ETTs, and for whom an informed consent was available. Excluded were infants with a single-lumen ETT.

Study Procedure

All infants who needed an ETT were intubated in the delivery room or in the NICU by a double-lumen tube (Uncuffed Tracheal Tube [Mallinckrodt Inc, Chih, Mexico]). This ETT has an extra small lumen for administration of exogenous surfactant or for measurements of distal pressures close to the carina. The inner diameter is similar to other ETTs, and the outer diameter has slight variation between different ETTs (eg, for inner diameter of 3 mm, the outer diameter of the ETT that we used is 4.5 mm, of the Portex Tracheal Tube [Smiths Medical Int, Kent, United Kingdom] 4.2 mm, and for the Vygon [Ecouen, France] 4.6 mm).

We monitored $ETCO_2$ in intubated infants by 2 capnographs simultaneously. The sidestream $DETCO_2$ was measured distally by a Microstream capnograph via a Microstream sampling line (Oridion Medical 1987 Ltd, Needham, MA). The mainstream $PETCO_2$ was measured via capnograph connected to the proximal end of the ETT (Philips IntelliVue patient monitor, Capnography Extension M3014A [Philips, Boeblingen, Germany]). Readings from the 2 methods were charted at the time of blood sampling for routine patient care via an indwelling arterial line and compared with $PaCO_2$ level (Omni AVL [Roche Diagnostic Gmbh, Graz, Austria]). Before each blood sampling, we ensured an adequate reading of $PETCO_2$ and a reliable waveform on the Microstream capnograph (continuous steady waveform of expired CO_2 throughout the ventilatory cycle) and cleared secretions from the side port of the ETT for $DETCO_2$ measurement (by inserting 5 mL of air). Microstream sampling lines blocked by secretions were replaced as needed.

We collected data on the patients' characteristics, type of pulmonary or cardiac disease, and severity of pulmonary disease (by oxygenation index [OI] defined as fractional inspired oxygen $\times$ mean airway pressure/PaO_2, and by the level of ventilation-perfusion mismatch assessed by PaO_2/partial pressure of O_2 in the alveoli (PAO_2) ratio). Severe lung disease was defined as PaO_2/PAO_2 ratio <0.3[17,20] or OI >10; mild to moderate lung disease was defined as PaO_2/PAO_2 ratio >0.3 and OI <10 (PAO_2 was calculated by fractional inspired oxygen $\times$ [barometric pressure $-$ 47] $-$ alveolar $PACO_2/0.8$). For the purpose of this abbreviated alveolar gas equation, alveolar $PACO_2$ was estimated by the $PaCO_2$. A bias $\leq$5 mm Hg was considered acceptable bias and $>$5 mm Hg an unacceptable bias.[9,10] The consistency of $ETCO_2$ monitoring (proximal and distal) within each patient was assessed by examining the relationship between the change in $PaCO_2$ and the change in $ETCO_2$ in consecutive samples.

Statistical Analysis

We evaluated the correlation of $dETCO_2$ and $pETCO_2$ and $PaCO_2$ by linear regression analysis and assessed the agreement between these measurements (bias [mean difference] and precision [SD of the differences]) by the Bland-Altman technique.[21] We evaluated the correlation between the changes in $PaCO_2$ and the simultaneous changes in $DETCO_2$ and $PETCO_2$ for consecutive measurements within each patient by linear regression analysis. Level of significance was set at $P < .05$. SigmaStat 2.03 (Chicago, IL) and the Minitab 12.23 (State College, PA) statistical software packages were used.

RESULTS

Twenty-seven infants participated in the study. Excluded were 9 comparable infants who were ventilated with a single-lumen ETT for technical reasons. A total of 222 measurements of $DETCO_2$ and 212 of $PETCO_2$ were analyzed. Table 1 shows the characteristics of the pa-

TABLE 1 **Patient Characteristics ($n = 27$)**

Characteristic	Value
Gestational age, median (range), wk	32.50 (24.80–40.80)
Birth weight, median (range), g	1835.00 (490.00–4790.00)
Age of enrollment, median (range), d	1.00 (1.00–26.00)
No. of observations (range)	8.00 (1.00–24.00)
pH, median (range)	7.34 (6.50–7.50)
F_{IO_2}, median (range)	0.31 (0.21–1.00)
Pa_{O_2}/PA_{O_2} ratio, median (range)	0.50 (0.06–2.38)
OI, median (range)	3.29 (0.63–23.0)
Primary diagnosis ($n = 27$ infants)	
Respiratory distress syndrome	19
Tracheo-esophageal fistula and esophageal atresia	3
Pneumonia	1
Primary pulmonary hypertension	1
Meconium aspiration syndrome	1
Hypoxic ischemic encephalopathy	1
Necrotizing enterocolitis	1

* F_{IO_2} indicates inspired oxygen fraction.
** Pa_{O_2}/PA_{O_2} alveolar/arterial oxygen tension ratio.
*** $OI = F_{IO_2} \times$ mean airway pressure/PA_{O_2}.

tients who participated in the study. All were on synchronized intermittent mandatory ventilation (SLE 2000 and 5000 [Specialized Laboratory Equipment Ltd, South Croydon, United Kingdom]).

The median (range) levels of $Paco_2$, $Detco_2$, and $Petco_2$ were 46.3 (24.5–99.7) mm Hg, 46.0 (20.0–98.0) mm Hg, and 37.0 (12.0–71.0) mm Hg, respectively.

Figure 1 shows the linear correlation between $Detco_2$ and $Petco_2$ with arterial Pco_2. Whereas the correlation coefficient (r) of $Detco_2$ and $Paco_2$ was adequate ($r = 0.72$, $P < .001$), that of the $Petco_2$ was poor ($r = 0.21$, $P < .005$).

Figure 2 presents the Bland-Altman plots of the differences between $Detco_2$ and $Petco_2$ and arterial CO_2. The mean difference (bias) and the SD of the differences (precision) for $Detco_2$ was -1.5 ± 8.7 mm Hg and for $Petco_2$ was -10.2 ± 13.7 mm Hg. The correlating medians (25th and 75th percentiles) were -1.1 (-5.6 and 2.7) and -10.3 (-16.0 and -0.8) mm Hg respectively. Although both $Detco_2$ and $Petco_2$ levels underestimated the $Paco_2$ level, $Detco_2$ was more accurate than $Petco_2$ as a noninvasive measure of $Paco_2$.

$Detco_2$ (21 samples) remained useful as a measure of $Paco_2$, whereas $Petco_2$ (19 samples) was distorted on the high range of $Paco_2$ levels ($\geq$60 mm Hg; $r = 0.77$, $P < .001$, and $r = 0.21$, $P = .38$; bias $\pm$ precision: -4.8 ± 7.9 and -33.3 ± 20.0 mm Hg respectively).

Thirteen infants were very low birth weight (VLBW; <1500 g), and 8 infants were <1000 g. The VLBW infants accounted for 84 observations. A subanalysis for these infants revealed a good linear correlation for $Detco_2$ and $Paco_2$ ($r = 0.72$, $P < .001$) as opposed to poor correlation of the $Petco_2$ ($r = 0.11$, $P = .32$). In the VLBW infants, the bias $\pm$ precision for $Detco_2$ was -0.3 ± 11.1 mm Hg and for $Petco_2$ was -14.8 ± 18.7 mm Hg.

Table 2 shows the effect of the severity of pulmonary disease (assessed by Pa_{O_2}/PA_{O_2} ratio or by OI) on the accuracy of $Detco_2$ and $Petco_2$ readings. We found that $Detco_2$ still correlated with $Paco_2$, but its bias increased with the severity of pulmonary disease.

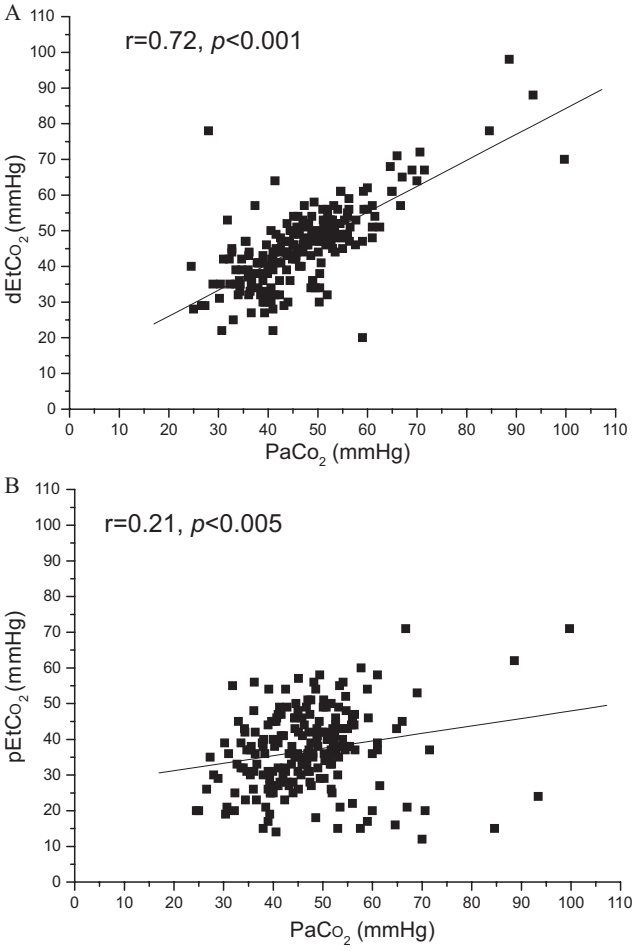

FIGURE 1
Correlation between $Detco_2$ (A) and $Petco_2$ (B) with $Paco_2$.

We evaluated the changes in $Paco_2$ and the simultaneous changes in $Petco_2$ and $Detco_2$ for consecutive measurements within each patient. The mean change in $Paco_2$ was 0.12 ± 9.30 mm Hg and in $Detco_2$ was 0.90 ± 10.80 mm Hg ($r = 0.49$, $P < .001$). Mean change in $Petco_2$ was -0.02 ± 8.50 mm Hg ($r = 0.17$, $P < .05$) compared with the simultaneous changes in $Paco_2$.

DISCUSSION

We found that $Detco_2$ was an accurate and reliable noninvasive method for estimating $Paco_2$. It had a good correlation with $Paco_2$ ($n = 222$, $r = 0.72$, $P < .001$), which was slightly lower compared with mainstream $Petco_2$ as previously reported for NICU infants by Rozycki et al[10] ($n = 411$, $r = 0.83$, $P < .001$). The bias we report for $Detco_2$ (-1.5 ± 8.7 mm Hg) was even smaller than that reported by Rozycki et al for mainstream $Petco_2$ (-6.9 ± 6.9 mm Hg), and was well less than 5 mm Hg, which is considered within the good agreement range.[9,10] In our study, the correlation and the agreement of $Detco_2$ with $Paco_2$ were better than those for

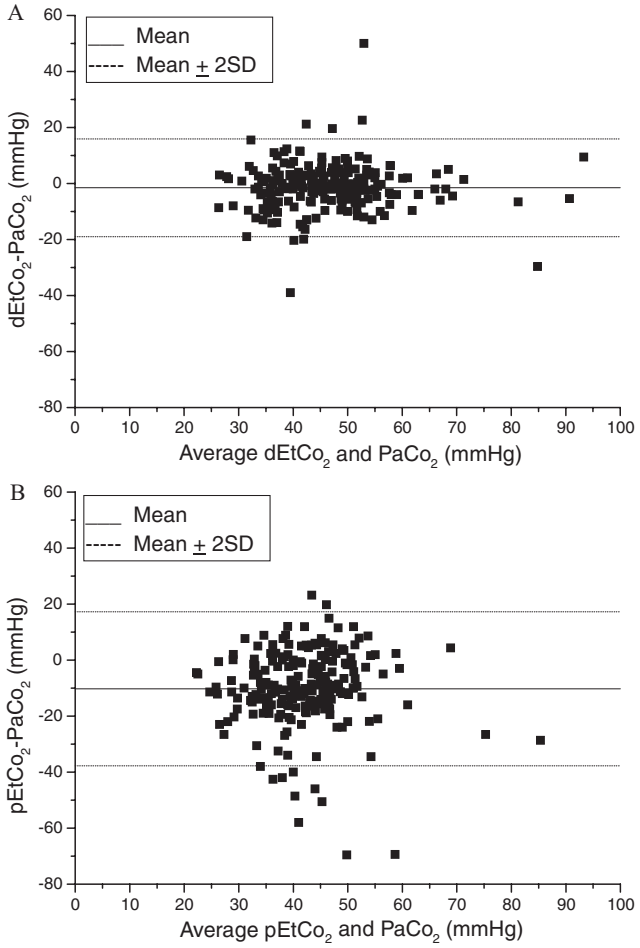

FIGURE 2
Bland-Altman plots of the difference between $Paco_2$ and $Detco_2$ (A) and $Petco_2$ (B).

mainstream $Petco_2$. Several investigators reported similar results for distal and proximal sidestream $ETCO_2$,[18,19] whereas others reported comparable accuracy of distal and proximal mainstream $ETCO_2$[11]; however, neither of these studies measured $Detco_2$ by a double-lumen ETT or used the Microstream technique. Our study results regarding the mainstream $Petco_2$, which differ from reported better results for that method,[10] should be interpreted with caution and could result from different conditions in the different studies reflected by mixture of patients, severity of their lung disease, levels of leak around the ETT, and instrumentation used for measurements. Although the bias of the $Detco_2$ was relatively small in our study, the 95% CIs were relatively wide in our study as well as in the other studies.[10] Thus, $ETCO_2$ should not replace $Paco_2$ measurements but rather serve as a complementary tool for trending and for real-time continuous assessment of the CO_2 levels. We suggest correlating the $ETCO_2$ and the $Paco_2$ for monitoring in the individual patient.

Severity of disease was reported to affect the accuracy of capnometry/capnography in several studies. The more severe the ventilation-perfusion mismatch, the higher the difference between $ETCO_2$ and $Paco_2$.[9,20] Parenchymal lung disease with ventilation-perfusion mismatching is a common feature in NICUs. Sivan et al[20] reported that Pao_2/Pao_2 ratio >0.3 was associated with better agreement between $ETCO_2$ and $Paco_2$, and Hagerty et al[9] found a higher gradient between $ETCO_2$ and $Paco_2$ when comparing newborns with pulmonary disease and those who received mechanical ventilation for nonpulmonary conditions. Different results were reported by other investigators. Tingay et al[17] found that the $ETCO_2$ bias was independent of severity of lung disease, and Rozycki et al[10] reported that measures of degree of lung disease had little influence on the degree of bias. In our study, the agreement of $Detco_2$ and $Paco_2$ decreased, but the bias in patients with Pao_2/Pao_2 ratio <0.3 remained <5 mm Hg. We assessed whether the level of $Paco_2$ affected the accuracy of $ETCO_2$ readings and found it to affect the $Petco_2$ much more than the $Detco_2$, which remained with adequate agreement with the $Paco_2$. Rosycki et al[10] did not find that the accuracy of $Petco_2$ was affected by the $Paco_2$ level. Our findings suggest that $Detco_2$ as evaluated in our study could be used as a reliable, noninvasive method for $Paco_2$ assessment in the full spectrum of NICU patients.

In our study, we used a novel method that combined 2 techniques. We used the Microstream sidestream capnography, which was used previously only in 2 studies of newborns,[9,17] and for the first time we used a double-lumen ETT for that purpose, which allowed continuous measurement of $Detco_2$ via its extra lumen. The intention of the Microstream technique is to improve the accuracy of sidestream capnography. Microstream capnography uses a sampling flow rate of 50 mL/min, approximately one third of that used by previous studies with conventional sidestream systems. This low flow

TABLE 2 **Relation Between $ETCO_2$ Values and Severity of Lung Disease**

Parameter	Severity of Lung Disease					
	Mild to Moderate			Severe		
	Mean (SD)	*r*	*P*	Mean (SD)	*r*	*P*
Pao_2/Pao_2 ratio	>0.3 (*n* = 168)			≤0.3 (*n* = 63)		
$Detco_2$–$Paco_2$	−0.24 ± 7.30	0.74	<.001	−4.20 ± 10.50	0.64	<.001
$Petco_2$–$Paco_2$	−9.10 ± 14.00	0.07	.340	−12.50 ± 12.50	0.35	<.010
OI	<10 (*n* = 216)			≥10 (*n* = 16)		
$Detco_2$–$Paco_2$	−0.70 ± 8.20	0.69	<.001	−9.00 ± 8.10	0.77	<.001
$Petco_2$–$Paco_2$	−9.80 ± 13.90	0.13	.070	−13.00 ± 9.80	0.52	.054

All CO_2 levels in mm Hg.

rate reduces the competition for tidal volume and also decreases condensation within the system. Because of the highly CO_2-specific infrared source, the sample cell uses a much smaller volume (15 μL) that permits a low flow rate without compromising response rate or accuracy. These features preserve accuracy by preventing mixing of the small inspiratory and expiratory volumes observed in newborns while rapid response time (<180 milliseconds) is maintained by laminar gas flow throughout the breathing circuit.[22] The new low-flow sidestream capnograph (Oridion Medical 1987 Ltd) was tested when connected to the side port of the proximal ETT by Hagerty et al,[9] and they reported a gradient of -3.4 ± 2.4 mm Hg in ventilated infants without pulmonary disease and -7.4 ± 3.3 mm Hg in those with pulmonary disease. Tingay et al[17] also used the Microstream technique (Agilent Microstream system, Andover, MA) for monitoring P_{ETCO_2} in infants during neonatal transport. They reported that the P_{ETCO_2} had a linear relation with $Paco_2$ but had an unacceptable underestimation of $Paco_2$ (-8.2 ± 5.2 mm Hg) and did not trend reliably over time within an individual patient. In our study, using the Microstream technique but measuring D_{ETCO_2} via the side port of the double-lumen ETT, the agreement with $Paco_2$ improved in infants with both mild and severe pulmonary disease (-0.24 ± 7.3 and -4.2 ± 10.5 mm Hg respectively). The improvement could be related to distal measurements of $ETCO_2$. This technique, which measures $ETCO_2$ close to the carina, may be less affected by the ventilatory circuit flow and leaks around the uncuffed ETTs used in neonates. The values of D_{ETCO_2} as opposed to P_{ETCO_2} are not affected by flow sensors that are commonly used nowadays with the new ventilators (flow sensors prevented the use of P_{ETCO_2} in a few of our infants because of inadequate measurements).

There were several technical limitations to distal measurements. We had to use a double-lumen ETT, which is an approved tube but is slightly softer compared with some other tubes, thereby requiring the aid of a guide for some of the intubations. The extra lumen and the cannula are thin and may be occluded with secretions while continuously sampling $ETCO_2$. The main occlusions occurred at the proximal Microstream sampling line, which cannot be flushed with air to avoid damage to its filters. This limitation was partially solved by frequent changing of the sampling line. During sidestream sampling of CO_2, there is a constant leak in the ventilation system. We did not examine in our study the possible problems that this might cause in terms of accuracy of flow measurements. It is not possible to extrapolate our findings to modes of ventilation other than synchronized intermittent mandatory ventilation, such as patient-trigger ventilation, whereby the rates are more rapid and the tidal volumes are smaller. Charting of each pair of distal and proximal capnography was not blinded, and this is a potential for study bias.

Although there is no debate that noninvasive CO_2 assessment is important,[1–5] there is a debate regarding the preferred method. Rosycki et al[10] concluded that mainstream P_{ETCO_2} was as accurate but less precise than transcutaneous CO_2 monitoring as reported by Palmisano et al[23] ($r > 0.9$, bias of 1.79 ± 7.9 mm Hg). Tingay et al[17] concluded that transcutaneous CO_2 monitoring should be considered the preferred method for noninvasive CO_2 monitoring for neonatal transport. Their bias for transcutaneous CO_2 monitoring was 0.97 ± 5.33 mm Hg. The advantage of transcutaneous CO_2 monitoring should be weighed against those of $ETCO_2$: a much faster response time to changes in blood CO_2 levels, internal calibrating ability, and no thermal injury to the fragile skin of the newborn.[24] With the advantages of D_{ETCO_2} monitoring, the conclusions regarding the preferred techniques for noninvasive CO_2 monitoring in neonates should be reconsidered.

Because data regarding the waveforms (termed capnography) were not recorded and analyzed in our study, it is not possible to know whether adding some form of wave analysis to the $ETCO_2$ value as performed by Hagerty et al[9] would have improved our ability to monitor $ETCO_2$ more precisely. Thus, some of the differences between capnography and $Paco_2$ could be attributed to failure to obtain a proper alveolar gas sample when a plateau was not fully achieved.

Although our study is the first to use distal Microstream capnography via double-lumen ETT in the NICU, more studies are needed to show the usefulness of this method in infants who weigh <1500 g and <1000 g. Our subanalysis for infants who weighed <1500 g (13 infants, 84 observations) revealed a good correlation and agreement between D_{ETCO_2} and a $Paco_2$ and poor for P_{ETCO_2}; however, the number of such infants was relatively small (only 8 infants weighed <1000 g); therefore, it does not have the power to answer this question in this population that may represent the majority of ventilated infants in future NICUs.

CONCLUSIONS

The novel method of measuring D_{ETCO_2} via a double-lumen ETT was found to have good correlation and agreement with $Paco_2$ and remained reliable in conditions of severe lung disease. D_{ETCO_2} was more accurate than the standard mainstream P_{ETCO_2} method as assessed in our study. The method is not invasive and thus is safe to be used even in the smallest infants. $ETCO_2$ does not replace $Paco_2$ but may be useful for trending and for real-time continuous screening of abnormal $Paco_2$ levels. Because noninvasive CO_2 monitoring may be of importance for the short-term and long-term outcome of intubated neonates and because the current available methods are limited, medical teams should consider the use of this noninvasive method of assessing $Paco_2$ in NICUs.

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