A Novel Method of Distal End-Tidal CO₂ Capnography in Intubated Infants: Comparison With Arterial CO₂ and With Proximal Mainstream End-Tidal CO₂

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ABSTRACT

OBJECTIVE. The objective of this study was to evaluate a novel method of distal end-tidal CO₂ capnography by comparison with PaCO₂ and with the more standard method that measures mainstream proximal end-tidal CO₂ 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 PaCO₂. Sidestream distal end-tidal CO₂ was measured by a Microstream capnograph via the extra port of a double-lumen endotracheal tube. Mainstream proximal end-tidal CO₂ 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 CO₂ and proximal end-tidal CO₂, respectively. Distal compared with proximal end-tidal CO₂ had a better correlation with PaCO₂ and a better agreement with PaCO₂. The accuracy of distal end-tidal CO₂ decreased, but it remained a useful measure of PaCO₂ in the high range of PaCO₂ (≥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 CO₂ and PaCO₂ and poor correlation and agreement for proximal end-tidal CO₂.

CONCLUSIONS. Distal end-tidal CO₂ measured via a double-lumen endotracheal tube was found to have good correlation and agreement with PaCO₂, remained reliable in conditions of severe lung disease, and was more accurate than the standard mainstream proximal end-tidal CO₂.

CONTINUOUS NONINVASIVE MONITORING of CO₂ levels in the NICU is important because it may protect infants from the complications of hypocarbia and hypercarbia and avoid extra blood sampling, which may cause anemia, discomfort, and pain. Capnography, which displays the level and the waveform of CO₂ in exhaled air, provides information on cell metabolism, blood perfusion, and alveolar ventilation.

The use of end-tidal CO₂ (ETCO₂) 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. Recently, it was also introduced to NICUs. 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.

It is possible to measure ETCO₂ by mainstream or sidestream capnometry/capnography. Mainstream capnometry was found to be more accurate; 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 ETCO2 may have an advantage of possible use in the distal part of the ETT. Distal ETCO2 (DETCO2) may be less susceptible to air leak or mixing of the measured ETCO2 with inhaled air. Furthermore, there is now a new technology, the Microstream technique, that can also improve the accuracy of sidestream ETCO2 in newborns.9,17 To take additional advantage of the benefits of distal measurement of ETCO2, we used an innovative technique. Instead of inserting a catheter into the ETT to sample DETCO2, 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 ETCO2 monitoring.

We hypothesized that DETCO2 as measured by the Microstream technique via a double-lumen ETT would have better or at least comparable correlation and agreement with PaCO2 as the proximal end-tidal CO2 (PETCO2) measured by mainstream capnography. The aim of our study was to evaluate this novel method of measuring DETCO2 by comparison with PaCO2 and with the more standard method that measures mainstream PETCO2 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 PETCO2 and DETCO2 monitors, and the measurements were compared with PaCO2 drawn for patient care. Measurements of DETCO2 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 DETCO2 with the gold standard of PaCO2. The secondary outcome measure was to compare these findings with the more standard and commonly used method of mainstream PETCO2.

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 ETCO2 in intubated infants by 2 capnographs simultaneously. The sidestream DETCO2 was measured distally by a Microstream capnograph via a Microstream sampling line (Oridion Medical 1987 Ltd, Needham, MA). The mainstream PETCO2 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 PaCO2 level (Omni AVL [Roche Diagnostic Gmbh, Graz, Austria]). Before each blood sampling, we ensured an adequate reading of PETCO2 and a reliable waveform on the Microstream capnograph (continuous steady waveform of expired CO2 throughout the ventilatory cycle) and cleared secretions from the side port of the ETT for DETCO2 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 × mean airway pressure/PaO2, and by the level of ventilation-perfusion mismatch assessed by PaO2/partial pressure of O2 in the alveoli [PAO2] ratio). Severe lung disease was defined as PAO2/PaO2 ratio <0.317,20 or OI >10; mild to moderate lung disease was defined as PAO2/PaO2 ratio >0.3 and OI <10 (PaO2 was calculated by fractional inspired oxygen × [barometric pressure – 47] – alveolar PaO2/0.8). For the purpose of this abbreviated alveolar gas equation, alveolar PaO2 was estimated by the PaCO2. A bias ≤5 mm Hg was considered acceptable bias and >5 mm Hg an unacceptable bias.9,10 The consistency of ETCO2 monitoring (proximal and distal) within each patient was assessed by examining the relationship between the change in PaCO2 and the change in ETCO2 in consecutive samples.

Statistical Analysis

We evaluated the correlation of dETCO2 and pETCO2 and PaCO2 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.31 We evaluated the correlation between the changes in PaCO2 and the simultaneous changes in DETCO2 and PETCO2 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 DETCO2 and 212 of PETCO2 were analyzed. Table 1 shows the characteristics of the pa-
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 PaCO2, DETCO2, and PETCO2 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 DETCO2 and PETCO2 with arterial PCO2. Whereas the correlation coefficient (r) of DETCO2 and PaCO2 was adequate (r = 0.72, P < .001), that of the PETCO2 was poor (r = 0.21, P < .005).

Figure 2 presents the Bland-Altman plots of the differences between DETCO2 and PETCO2 with arterial PCO2. The mean difference (bias) and the SD of the differences (precision) for DETCO2 was −1.5 ± 8.7 mm Hg and for PETCO2 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 DETCO2 and PETCO2 levels underestimated the PaCO2 level, DETCO2 was more accurate than PETCO2 as a noninvasive measure of PaCO2.

DETCO2 (21 samples) remained useful as a measure of PaCO2, whereas PETCO2 (19 samples) was distorted on the high range of PaCO2 levels (≥60 mm Hg; r = 0.77, P < .001, and r = 0.21, P = .38; bias ± 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 DETCO2 and PaCO2 (r = 0.72, P < .001) as opposed to poor correlation of the PETCO2 (r = 0.11, P = .32). In the VLBW infants, the bias ± precision for DETCO2 was −0.3 ± 11.1 mm Hg and for PETCO2 was −14.8 ± 18.7 mm Hg.

Table 2 shows the effect of the severity of pulmonary disease (assessed by PaO2/PaO2 ratio or by OI) on the accuracy of DETCO2 and PETCO2 readings. We found that DETCO2 still correlated with PaCO2, but its bias increased with the severity of pulmonary disease.

We evaluated the changes in PaCO2 and the simultaneous changes in PETCO2 and DETCO2 for consecutive measurements within each patient. The mean change in PaCO2 was 0.12 ± 9.30 mm Hg and in DETCO2 was 0.90 ± 10.80 mm Hg (r = 0.49, P < .001). Mean change in PETCO2 was −0.02 ± 8.50 mm Hg (r = 0.17, P < .05) compared with the simultaneous changes in PaCO2.

DISCUSSION

We found that DETCO2 was an accurate and reliable noninvasive method for estimating PaCO2 . It had a good correlation with PaCO2 (n = 222, r = 0.72, P < .001), which was slightly lower compared with mainstream PETCO2 as previously reported for NICU infants by Rozycki et al10 (n = 411, r = 0.83, P < .001). The bias we report for DETCO2 (−1.5 ± 8.7 mm Hg) was even smaller than that reported by Rozycki et al for mainstream PETCO2 (−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 DETCO2 with PaCO2 were better than those for
Several investigators reported similar results for distal and proximal sidestream ETCO₂, whereas others reported comparable accuracy of distal and proximal mainstream ETCO₂; however, neither of these studies measured DETCO₂ by a double-lumen ETT or used the Microstream technique. Our study results regarding the mainstream PETCO₂, which differ from reported better results for that method, 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 DETCO₂ was relatively small in our study, the 95% CIs were relatively wide in our study as well as in the other studies. Thus, ETCO₂ should not replace PaCO₂ measurements but rather serve as a complementary tool for trending and for real-time continuous assessment of the CO₂ levels. We suggest correlating the ETCO₂ and the PaCO₂ 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 ETCO₂ and PaCO₂. Parenchymal lung disease with ventilation-perfusion mismatching is a common feature in NICUs. Sivan et al reported that PaO₂/PAO₂ ratio >0.3 was associated with better agreement between ETCO₂ and PaCO₂, and Hagerty et al found a higher gradient between ETCO₂ and PaCO₂ 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 found that the DETCO₂ bias was independent of severity of lung disease, and Rozycki et al reported that measures of degree of lung disease had little influence on the degree of bias. In our study, the agreement of DETCO₂ and PaCO₂ decreased, but the bias in patients with PaO₂/PAO₂ ratio <0.3 remained <5 mm Hg. We assessed whether the level of PaCO₂ affected the accuracy of ETCO₂ readings and found it to affect the PETCO₂ much more than the DETCO₂, which remained with adequate agreement with the PaCO₂. Rosycki et al did not find that the accuracy of PETCO₂ was affected by the PaCO₂ level. Our findings suggest that DETCO₂ as evaluated in our study could be used as a reliable, noninvasive method for PaCO₂ 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, and for the first time we used a double-lumen ETT for that purpose, which allowed continuous measurement of DETCO₂ 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild to Moderate</th>
<th>Severe</th>
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<tr>
<td></td>
<td>Mean (SD)</td>
<td>r</td>
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<tr>
<td>PaO₂/PAO₂ ratio</td>
<td>&gt;0.3 (n = 168)</td>
<td>0.74</td>
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<tr>
<td>DETCO₂–PaCO₂</td>
<td>−0.24 ± 7.30</td>
<td>0.07</td>
</tr>
<tr>
<td>PETCO₂–PaCO₂</td>
<td>−9.10 ± 14.00</td>
<td>0.07</td>
</tr>
<tr>
<td>OI</td>
<td>&lt;10 (n = 216)</td>
<td>0.07</td>
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<tr>
<td>DETCO₂–PaCO₂</td>
<td>−0.70 ± 8.20</td>
<td>0.69</td>
</tr>
<tr>
<td>PETCO₂–PaCO₂</td>
<td>−9.80 ± 13.90</td>
<td>0.13</td>
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All CO₂ levels in mm Hg.
rate reduces the competition for tidal volume and also decreases condensation within the system. Because of the highly CO2-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 throughout the breathing circuit. 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 al19 and they reported a gradient of \(-3.4 \pm 2.4 \text{ mm Hg}\) in ventilated infants without pulmonary disease and \(-7.4 \pm 3.3 \text{ mm Hg}\) in those with pulmonary disease. Tingay et al17 also used the Microstream technique (Agilent Microstream system, Andover, MA) for monitoring PETCO2 in infants during neonatal transport. They reported that the PETCO2 had a linear relation with Paco2 but had an unacceptable underestimation of Paco2 (\(-8.2 \pm 5.2 \text{ mm Hg}\)) and did not trend reliably over time within an individual patient. In our study, using the Microstream technique but measuring DETCO2 via the side port of the double-lumen ETT, the agreement with Paco2 improved in infants with both mild and severe pulmonary disease (\(-0.24 \pm 7.3 \text{ and } -4.2 \pm 10.5 \text{ mm Hg}\) respectively). The improvement could be related to distal measurements of ETCO2. This technique, which measures ETCO2 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 DETCO2 as opposed to PETCO2 are not affected by flow sensors that are commonly used nowadays with the new ventilators (flow sensors prevented the use of PETCO2 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 ETCO2. 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 CO2, 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 CO2 assessment is important,1-4 there is a debate regarding the preferred method. Rosycki et al10 concluded that mainstream PETCO2 was as accurate but less precise than transcutaneous CO2 monitoring as reported by Palmisano et al21 (\(r > 0.9\), bias of 1.79 \pm 7.9 \text{ mm Hg}\). Tingay et al17 concluded that transcutaneous CO2 monitoring should be considered the preferred method for noninvasive CO2 monitoring for neonatal transport. Their bias for transcutaneous CO2 monitoring was 0.97 \pm 5.33 \text{ mm Hg}. The advantage of transcutaneous CO2 monitoring should be weighed against those of ETCO2: a much faster response time to changes in blood CO2 levels, internal calibrating ability, and no thermal injury to the fragile skin of the newborn.24 With the advantages of DETCO2 monitoring, the conclusions regarding the preferred techniques for noninvasive CO2 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 ETCO2 value as performed by Hagerty et al19 would have improved our ability to monitor ETCO2 more precisely. Thus, some of the differences between capnography and Paco2 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 DETCO2 and a Paco2 and poor for PETCO2; 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 DETCO2 via a double-lumen ETT was found to have good correlation and agreement with Paco2 and remained reliable in conditions of severe lung disease. DETCO2 was more accurate than the standard mainstream PETCO2 method as assessed in our study. The method is not invasive and thus is safe to be used even in the smallest infants. ETCO2 does not replace Paco2 but may be useful for trending and for real-time continuous screening of abnormal Paco2 levels. Because noninvasive CO2 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 Paco2 in NICUs.

**ACKNOWLEDGMENTS**

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