Impact of Continuous Capnography in Ventilated Neonates: A Randomized, Multicenter Study

Amir Kugelman, MD[1,2], Agenta Golan, MD[3], Arieh Riskin, MD, MHA[1], Irit Shoris, RN, BA[1], Michal Ronen, PhD[4], Nelly Qumqam, RN[5], David Bader, MD, MHA[1], and Ruben Bromiker, MD[5]

Objective To compare the time spent within a predefined safe range of CO_2 (30-60 mmHg) during conventional ventilation between infants who were monitored with distal end-tidal CO_2 ($dETCO_2$, or capnography) and those who were not.

Study design For this randomized, controlled multicenter study, ventilated infants with a double-lumen endotracheal tube were randomized to 1 of 2 groups: the open (monitored) group, in which data from the capnograph were recorded, displayed to the medical team, and used for patient care, and the masked group, in which data from the capnograph were recorded. However, the measurements were masked and not available for patient care. $dETCO_2$ was compared with $PaCO_2$ measurements recorded for patient care.

Results Fifty-five infants (25 open, 30 masked) participated in the study (median gestational age, 28.6 weeks; range, 23.5-39.0 weeks). The 2 groups were comparable. $dETCO_2$ was in good correlation ($r = 0.73$; $P < .001$) and adequate agreement (mean $\pm$ SD of the difference, 3.0 $\pm$ 8.5 mmHg) with $PaCO_2$. Compared with infants in the masked group, those in the monitored group had significantly ($P = .03$) less time with an unsafe $dETCO_2$ level (high: 3.8% vs 8.8% or low: 3.8% vs 8.9%). The prevalence of intraventricular hemorrhage or periventricular leukomalacia rate was lower in the monitored group ($P = .02$) and was significantly ($P < .05$) associated with the independent factors $dETCO_2$ monitoring and gestational age.

Conclusion Continuous $dETCO_2$ monitoring improved control of CO_2 levels within a safe range during conventional ventilation in a neonatal intensive care unit. *(J Pediatr 2016;168:56-61).*

Trial registration ClinicalTrials.gov: NCT01572272.

C apnography, which displays the level and the waveform of CO_2 in exhaled air, provides information on cell metabolism, lung perfusion, and alveolar ventilation.[1] The use of end-tidal CO_2 ($ETCO_2$) for monitoring and for verifying endotracheal tube (ETT) position is a common practice in the operating room and in adult and pediatric intensive care units.[1] Currently, capnography is not commonly used in the neonatal intensive care unit (NICU) because of technical problems (eg, leakage around uncuffed ETTs, difficulty achieving adequate CO_2 waveforms in tachypneic premature infants) and its relative inaccuracy in conditions of ventilation–perfusion mismatch.[2,3]

Sampling breath close to the carina by measuring distal $ETCO_2$ ($dETCO_2$), known as distal capnography, may be less susceptible to air leak and/or mixing of the measured $ETCO_2$ with inhaled air. Kugelman et al[4] demonstrated that $dETCO_2$ measured by Microstream capnography technology (Covidien, Respiratory and Monitoring Solutions, Jerusalem, Israel) via a double-lumen ETT had as good or better correlation and agreement with $PaCO_2$ as mainstream capnography.[5]

The main goal of continuous noninvasive monitoring of CO_2 levels in the NICU is to protect ventilated infants from hypocarbia and hypercarbia.[6-9] Previous studies of $ETCO_2$ and of transcutaneous CO_2 monitoring were observational assessments of the feasibility of continuous noninvasive monitoring of CO_2, and of its agreement and correlation with $PaCO_2$.[3-5,10-16] We hypothesized that continuous $dETCO_2$ could protect ventilated infants in the NICU from hypocarbia and hypercarbia. The aim of the present study was to compare the time spent within a predefined safe range of CO_2 during conventional ventilation (CV) in infants who were monitored with $dETCO_2$ and those who were not.

ABG	Arterial blood gas	IVH	Intraventricular hemorrhage
BW	Birth weight	NICU	Neonatal intensive care unit
CV	Conventional ventilation	OI	Oxygenation index
$dETCO_2$	Distal end-tidal CO_2	PAO_2	Alveolar PO_2
$ETCO_2$	End-tidal CO_2	PVL	Periventricular leukomalacia
ETT	Endotracheal tube	VLBW	Very low birth weight
GA	Gestational age		

Methods

This randomized controlled study was conducted at 3 university-affiliated tertiary NICUs. Ventilated infants with a double-lumen ETT were randomized to either: (1) the open monitored (study) group, in which data from the capnograph were recorded, displayed to the medical team, and used for patient care; or (2) the masked (control) group, in which data from the capnograph were recorded. The measurements were masked and not available for patient care. The study was approved by the Israeli Ministry of Health's Review Board.

Our primary outcome measure was to compare the time spent within a predefined safe range of CO_2 (30 mmHg $<$ PCO_2 $<$ 60 mmHg),[17-21] during CV. An adequate (permissive) range of PCO_2 was defined as 45-55 mmHg.

The study cohort comprised all infants who met the inclusion criteria: (1) intubated with a double-lumen ETT and on CV; (2) signed informed consent from a parent; and (3) expected to provide at least 3 pairs of $PaCO_2$ and $ETCO_2$ measurements. Infants with a single-lumen ETT and those ventilated with high-frequency ventilation were excluded.

All infants who required mechanical ventilation were intubated in the delivery room or in the NICU with a double-lumen uncuffed ETT (Mallinckrodt Inc, Covidien IIc, Mansfield, Massachusetts). This ETT has an extra-small lumen designed originally for surfactant administration that we have used for measurements of $dETCO_2$ close to the carina.

Eligible infants were randomized, stratified by center, according to a pre-prepared list for assignment into the open or masked group. Masking of the capnography display was achieved using a designated cover for the monitor's screen, allowing the operator to watch only the capnography tracing, to ensure adequate measurements and determine the need to change the CO_2 sampling line while not seeing the numerical data.

$ETCO_2$ was measured with a Capnostream 20p bedside monitor (Covidien Respiratory and Monitoring Solutions, Jerusalem, Israel). Readings in the open group were charted at the time of blood sampling for routine patient care via an indwelling arterial line and compared with $PaCO_2$ levels (Omni AVL; Roche Diagnostic, Graz, Austria). Before each blood sampling, we ensured an adequate $dETCO_2$ reading and a reliable waveform on the Microstream capnograph, and cleared secretions from the side port of the ETT by inserting 5 mL of air.

During the study, the medical team recorded the following: changes in the ventilation variables, number and values of arterial blood gas (ABG) measurements, number of red blood cell transfusions, and number of chest radiographs. Additional clinical data were obtained from the medical record, including patient characteristics, type of pulmonary or cardiac disease, vital signs, blood transfusions, hematocrit at discharge, sepsis events, necrotizing enterocolitis, head ultrasound findings (intraventricular hemorrhage [IVH] or periventricular leukomalacia [PVL]), bronchopulmonary dysplasia[22] with target oxygen saturation >90% at 36 weeks corrected gestational age (GA), duration of mechanical ventilation, and length of stay.

Severity of pulmonary disease, assessed based on oxygenation index (OI), defined as fraction of inspired oxygen × mean airway pressure/PaO_2, and by the level of ventilation–perfusion mismatch measured by PaO_2/alveolar PO_2 (PAO_2), was recorded. Severe lung disease was defined as an arterial/alveolar oxygen tension (PaO_2/PAO_2) ratio <0.3[13,23] or an OI >10; mild to moderate lung disease was defined as a PaO_2/PAO_2 ratio >0.3 and an OI <10 (PAO_2 was calculated by fraction of inspired oxygen × [barometric pressure − 47] − alveolar PCO_2/0.8). For the purpose of this abbreviated alveolar gas equation, alveolar PCO_2 was estimated by the $PaCO_2$. A bias $<$ 5 mmHg was considered acceptable, and >5 mmHg was considered unacceptable.[3-5]

Statistical Analyses

The sample size calculation for the primary outcome (percentage of time within the predefined safe range of CO_2) was based on our previous study.[4] Using the 2-sided Mann-Whitney U test, we estimated that a sample size of 30 infants in each group was needed to have a >80% likelihood of detecting a 15% difference between the open monitored and masked groups ($\alpha <0.05$).

To analyze the main outcome of being in the safe range of CO_2 and the variable of $ETCO_2$ monitoring, we performed stratification by weight, performing the foregoing analysis separately for the subgroup of infants with birth weight (BW) <1500 g. Bivariate regression analysis was performed for each GA or BW separately with the mode of the monitoring (open or masked) for the outcome of IVH and PVL. For continuous variables, the 2-sample unpaired t test was used for variables with normal distribution, and the Mann-Whitney rank-sum test was used when distributions were skewed. Differences in categorical variables were tested using the χ^2 or Fisher exact test as appropriate. The correlation of $dETCO_2$ and $PaCO_2$ was evaluated by linear regression analysis, and the agreement between these measurements (bias [mean difference] and precision [SD of the difference]) was assessed using the Bland-Altman technique for multiple observations.[24] The level of significance was set at $P < .05$. MATLAB version 14b (Mathworks, Natick, Massachusetts) was used for all analyses except the regression analysis, which was done using SigmaStat version 2.03 (Systat Software, San Jose, California).

Results

Infants were enrolled between February 2013 and October 2014. Of 68 eligible infants, 66 were randomized to the open or masked group (Figure 1; available at www.jpeds.com), and 2 were excluded owing to parental refusal. Three dropped out of the study because they had less than 3 ABG measurements while ventilated, and 8 were not included in