

Accuracy of a New Low-flow Sidestream Capnography Technology in Newborns: A Pilot Study

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OBJECTIVE:

To evaluate the accuracy of a new low-flow sidestream capnography technology and analyze components of the capnogram in mechanically ventilated newborns with and without pulmonary disease.

METHODS:

Twenty patients were prospectively identified. Eligible infants were mechanically ventilated and had an indwelling arterial catheter. Two groups were identified: newborns who were receiving mechanical ventilation for pulmonary diseases, and newborns who were receiving postoperative mechanical ventilation for nonpulmonary conditions. End-tidal CO₂ (PetCO₂) was measured for 1-minute pre- and post-arterial blood sampling, and PetCO₂ and PaCO₂ were compared for each patient. Eight quantitative waveform parameters were also measured on all patients.

RESULTS:

Newborns in the pulmonary group ($n = 13$) (persistent pulmonary hypertension of the newborn/meconium aspiration syndrome, respiratory distress syndrome, pneumonia) and newborns in the control group ($n = 7$) were matched for birth weight, gestational age, and postnatal age. PetCO₂–PaCO₂ Gradient values were higher in the pulmonary group (7.4 ± 3.3 mm Hg) than controls (3.4 ± 2.4 mm Hg). Four waveform parameters (ascending slope, alveolar angle, alpha angle, descending angle) were identified, which independently differentiated patients with pulmonary disease from controls.

CONCLUSIONS:

Low-flow capnography with Microstream technology accurately measured alveolar CO₂ in newborns without pulmonary disease, as demonstrated by normal PetCO₂–PaCO₂ gradients. The measured PetCO₂–PaCO₂ gradient, as expected, was significantly higher in newborns with pulmonary disease. We also identified four quantitative waveform parameters that may be useful in differentiating between mechanically ventilated newborn patients with and without lung disease.

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INTRODUCTION

Advancements in the treatment of neonatal respiratory failure, including exogenous surfactant,^{1,2} inhaled nitric oxide (iNO),^{3,4} and a growing repertoire of assisted ventilation strategies⁵ have decreased morbidity and mortality. Patient monitoring has played a critical role in the safe and effective application of these advanced therapies. Conventional monitoring of pulmonary function in the neonatal intensive care unit (NICU) has included pulse oximetry, transcutaneous oxygen and carbon dioxide measurements, flow-volume loops, and capillary or arterial blood gas analysis.

Capnography provides the continuous measurement of partial pressure of CO₂ in expired respiratory gases. Although this technology has become the standard of care for monitoring ventilatory status of patients in the operating room,⁶ the application of capnography to the neonatal population has been restricted by technical problems that affect the accuracy of measurements. Conventional high-flow (150 to 200 ml/min) sidestream capnography underestimates alveolar CO₂ due to the relatively low tidal volumes and rapid respiratory rates in newborns, resulting in falsely low end-tidal CO₂ (PetCO₂) readings.^{7–12} Mainstream capnography often competes for tidal volume in newborns due to increased dead space created by the airway adapter.

The CO₂ waveform (capnogram) has been characterized for adult patients with normal and abnormal pulmonary function.^{13–15} In newborns, CO₂ waveform slurring (spurious decrease in the slope of the ascending phase of the capnogram) occurs due to dilution of exhaled gas when small, rapid breath packets are measured in a relatively large sample cell.¹⁶ Condensed water and patient secretions may also impede both mainstream and conventional sidestream technologies. As a result of these limitations, most NICUs do not

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routinely perform capnography to assess and manage ventilatory status.

We performed a preliminary evaluation of a new low-flow (50 ml/min) sidestream capnography technology¹⁶ by determining its ability to accurately reflect the relationship between PetCO₂ and PaCO₂ in newborns with and without pulmonary disease. We hypothesized that infants without pulmonary disease would demonstrate a normal PetCO₂–PaCO₂ gradient, whereas newborns with pulmonary disease and increased dead space would demonstrate a widened PetCO₂–PaCO₂ gradient. In addition, we analyzed CO₂ waveform parameters and their alterations in diseased states, in the same population of infants.

METHODS

Patient Population

This study was performed at a single academic center, Children's Hospital–Boston, after institutional review board approval was obtained. Infants were enrolled from the NICU after parental consent from July 1999 to November 1999. Eligible infants were mechanically ventilated and had an indwelling arterial catheter. Patients receiving high-frequency ventilation were excluded. A complete review of each

infant's medical record was performed at the time of enrollment. Two groups were identified: Newborns in group A were mechanically ventilated for pulmonary disease, whereas those in group B were receiving postoperative mechanical ventilation for nonpulmonary disease.

Study Design

Twenty infants were prospectively identified. Capnography was performed through a side port in the proximal endotracheal tube adapter. PetCO₂ was measured for one minute pre- and post-arterial blood sampling one time on each enrolled infant. The exact time of the arterial blood gas sample was noted to facilitate accurate waveform comparison. Capnography data were recorded during scheduled arterial blood analysis, therefore no additional blood sampling was performed for the purposes of this study. Data were continuously recorded on a laptop computer at each infant's bedside. Respiratory gas sampling was performed using a low-flow (50 mL/min), sidestream, hand held device, Microcap by Oridion Medical Inc., which utilized Microstream™ sampling technology. Proprietary software for recording PetCO₂ and respiratory rate at 40 Hz was supplied by Oridion Medical Inc.

Table 1 Validation Data

No.	BW (g)	GA (wk)	PNA (d)	DX	Ventilatory support	ES	PaCO ₂ (mm Hg)	EtCO ₂ (mm Hg)	Et-a Gradient (mm Hg)
<i>Group A: infants with pulmonary disease</i>									
01	4500	40	1	MAS/PPHN	SIMV	Y	48	43	5
02	3800	40	1	MAS/PPHN	SIMV	Y	52	54	2
03	3600	39	1	MAS/PPHN	SIMV	N	52	42	10
04	3995	40	3	MAS/PPHN	SIMV	N	50	52	2
05	3745	38	9	MAS/PPHN	SIMV	N	54	44	10
06	2755	41	7	MAS/PPHN	SIMV	Y	54	42	12
07	2900	35	1	RDS	SIMV	Y	46	40	6
08	1040	28	10	RDS	SIMV	Y	41	37	4
09	2670	35	15	RDS	SIMV	Y	57	47	10
10	950	27	4	RDS	SIMV	Y	68	57	11
11	1080	28	3	RDS	SIMV	Y	45	38	7
12	1500	30	2	RDS	SIMV	Y	51	44	7
13	3950	40	3	Pneumonia	SIMV	N	46	35	11
<i>Group B: infants without pulmonary disease</i>									
14	3210	40	3	EA-TEF	SIMV	N	39	35	4
15	1860	30	5	NEC	SIMV	N	51	49	2
16	2300	37	6	EA-TEF	SIMV	N	46	40	6
17	3400	40	8	Metabolic acidosis	SIMV	N	51	45	6
18	3020	36	2	Perinatal depression	SIMV	N	38	38	0
19	4160	40	50	AVM (Parks-Webber)	SIMV	N	42	41	1
20	805	29	50	NEC	SIMV	N	33	35	2

PPHN, persistent pulmonary hypertension of the newborn; MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome; EA-TEF, esophageal atresia with tracheo-esophageal fistula; NEC, necrotizing enterocolitis; CAVC, complete atrioventricular canal; AVM, arteriovenous malformation; BW, birth weight; GA, gestational age; PNA, postnatal age; DX, primary diagnosis; ES, exogenous surfactant; PaCO₂, arterial CO₂; EtCO₂, end-tidal CO₂; Et-a Gradient, end-tidal-arterial CO₂ gradient.

Table 2 Demographic Data

Characteristic	Group A (pulmonary conditions)	Group B (nonpulmonary conditions)	<i>p</i> -Value
BW, g	2807 ± 1271	2679 ± 1113	0.83
GA, wk	35.5 ± 5.4	36.0 ± 4.7	0.82
PNA, d	4.6 ± 4.2	17.7 ± 22.1	0.17
PaCO ₂ , mm Hg	51.1 ± 6.7	42.9 ± 6.8	0.02
EtCO ₂ , mm Hg	44.2 ± 6.7	40.4 ± 5.2	0.21
Et-a Gradient, mm Hg	7.4 ± 3.3	3.0 ± 2.4	< 0.01

Number of patients: Group A (*n* = 13), Group B (*n* = 7).
 See Table 1 for abbreviations.
p-Values were based on two-sample Student *t*-tests. Values represent the mean ± standard deviation.

Waveform Parameters

PetCO₂ was defined as the maximum end-expiratory CO₂ recorded during the time of the arterial blood gas sampling. To determine the ascending slope the middle point, whose value is the average of the minimum and maximum of the waveform on that slope, was located. The slope was calculated between two points, located on the opposite sides of the middle point at a temporal distance that equaled a given fraction (0.025) of a single respiratory cycle. The graphic calibration for making the slope unitless was done according to previously published work,¹⁷ and was taken at 1.25 mm/50 msec and 1.52 mm/1 mm Hg. The ascending angle was calculated as the arctangent of the slope. In a similar fashion, the descending slope and angle were calculated. The alveolar slope was calculated as the average slope between the maximum end-expiratory CO₂ (EtCO₂), immediately before the start of the descending slope, and a point 200 msec before the maximum. The alveolar angle was calculated as the arctangent of the slope. By geometrical calculations, the alpha angle equals 180 minus the ascending angle plus the alveolar angle. These measured parameters were averaged over a group of cycles whose respiratory rates differed by no more than six breaths per minute. All waveform parameters represent a mean value. Out of range values were excluded in calculating the mean values in the following manner: first, all results were averaged and the standard deviations (SDs) were calculated. Then a second averaging was performed using only those values that were within 2 SD from the average of the first step. Only machine-assisted breaths were considered for calculating the mean values. Machine-assisted breaths were defined as those waveforms having amplitude of >80% of the mean amplitude value for each patient and a respiratory rate of <150 breaths per minute. These criteria helped exclude background noise waveforms from analysis.

Statistical Analysis

The Kolmogorov-Smirnov goodness-of-fit test revealed no significant departures from a normal (Gaussian-shaped) distribution for any of the continuous variables.¹⁸ Therefore, PaCO₂, PetCO₂, PetCO₂–Pa CO₂ gradient, birth weight, gestational age, and

postnatal age for group A (pulmonary disease) and group B (nonpulmonary disease) were compared with two-sample Student *t*-tests. Normal alveolar–arterial and PetCO₂–PaCO₂ gradients were defined as 0 to 5 mm Hg.¹¹ Waveform parameters were calculated as described above on all 20 patients receiving mechanical ventilation. Analysis of variance (ANOVA) using the Fisher least significant difference procedure for multiple comparisons was performed to compare waveform parameters between infants with respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn/meconium aspiration syndrome (MAS/PPHN), and controls.¹⁹ To determine which of the eight waveform parameters independently differentiated patients with pulmonary disease from controls, stepwise logistic regression was utilized. A backward stepwise multivariate procedure was utilized to determine variables in the final models with the likelihood ratio test as the measure of significance.²⁰ The SPSS software package (version 10.0, SPSS, Chicago, IL) was utilized for statistical analysis. Significance was defined for two-tailed values of *p* < 0.05.

RESULTS

Data were collected on 20 patients for PetCO₂–PaCO₂ gradients, 13 with and 7 without pulmonary disease. Waveform analysis was performed on 19 patients as the one infant with a primary diagnosis of pneumonia was excluded in the comparison of waveform parameters.

The 13 patients in group A had the following pulmonary diagnoses: MAS/PPHN (*n* = 6), RDS (*n* = 6), and pneumonia (*n* = 1). Patients in group B did not have pulmonary disease and served as controls (*n* = 7). Tables 1 and 2 show the key characteristics of each group. The groups were not significantly different with respect to birth weight, gestational age, postnatal age, or mode of ventilatory support. PaCO₂ values were higher in group A than B (51.1 ± 6.7 vs. 42.9 ± 6.8 mm Hg, *p* = 0.02), as these patients had underlying pulmonary disease and abnormal lung function. Mean PetCO₂–PaCO₂ gradients were significantly different between groups A and B, respectively (7.4 ± 3.3 vs. 3.0 ± 2.4 mm Hg,

Table 3 Waveform Parameter Data

Waveform parameter	Patient group	Mean	Standard deviation	<i>p</i> -Value
AS	RDS	7.57	0.91	0.15
	PPHN/MAS	8.37	3.04	0.05*
	Combined	7.97	2.18	0.04*
	Controls	5.00	3.98	
AA	RDS	82.42	0.88	<0.01*
	PPHN/MAS	82.30	2.51	<0.01*
	Combined	82.36	1.79	<0.01*
	Controls	74.50	7.39	
AR	RDS	55.52	2.43	0.07
	PPHN/MAS	56.87	2.64	0.29
	Combined	56.19	2.52	0.09
	Controls	58.62	3.43	
ALS	RDS	2.61	1.10	0.51
	PPHN/MAS	2.54	1.20	0.55
	Combined	2.58	1.10	0.45
	Controls	1.93	2.54	
ALA	RDS	63.95	11.91	0.04*
	PPHN/MAS	63.08	14.03	0.04*
	Combined	63.52	12.41	0.02*
	Controls	46.90	15.32	
ALPHA	RDS	97.58	0.88	<0.01*
	PPHN/MAS	97.70	2.51	<0.01*
	Combined	97.64	1.79	<0.01*
	Controls	105.51	7.39	
DS	RDS	−1.43	0.03	0.10
	PPHN/MAS	−1.44	0.04	0.08
	Combined	−1.44	0.03	0.03*
	Control	−1.38	0.23	
DA	RDS	−81.97	1.31	<0.01*
	PPHN/MAS	−82.52	2.47	<0.01*
	Combined	−82.25	1.91	<0.01*
	Control	−68.54	13.22	

AS, ascending slope; AA, ascending angle; AR, area ratio; ALS, alveolar slope; ALA, alveolar angle; ALPHA, alpha angle; DS, descending slope; DA, descending angle; RDS, respiratory distress syndrome; PPHN/MAS, persistent pulmonary hypertension of the newborn/meconium aspiration syndrome; Combined, RDS and MAS/PPHN.

p-Values are based on one-way ANOVA followed by the Fisher least significant difference procedure to adjust for multiple comparisons for RDS and PPHN/MAS compared to controls.

*Statistically significant.

$p < 0.01$), showing patients with pulmonary disease (group A) to have wider gradients.

Eight quantitative waveform parameters (ascending slope, ascending angle, area ratio, alveolar slope, alveolar angle, alpha angle, descending slope, descending angle) were measured for each patient (Table 3). Differences were noted between the pulmonary disease group and controls for six waveform parameters: ascending angle (82.36 vs. 74.50, $p < 0.01$), alpha angle (97.64 vs. 105.51, $p < 0.01$), and descending angle (−82.25 vs. −68.54, $p < 0.01$), ascending slope (7.97 vs. 5.00, $p = 0.04$), descending slope (−1.44 vs. −1.38, $p = 0.03$), and alveolar angle (63.52 vs. 46.90, $p = 0.02$). There were no significant differences between the pulmonary disease subgroups for any of the waveform parameters ($p > 0.40$ in each case). Of the six waveform parameters showing a difference between

groups, stepwise logistic regression identified four multivariate predictors that independently differentiated patients with pulmonary disease from controls: ascending slope ($p < 0.01$), alveolar angle ($p = 0.02$), alpha angle ($p < 0.01$), and descending angle ($p < 0.01$). Patients with pulmonary disease had a steeper ascending slope and larger alveolar angle, a smaller alpha angle, and a larger descending angle.

DISCUSSION

Capnography has become the standard of care for basic anesthesia monitoring for all intubated patients in the operating room, and PetCO₂ is commonly measured during mechanical ventilation of children in the intensive care unit. The extension of this technique to

intubated newborns has been limited by technical problems associated with mainstream and conventional high-flow sidestream technology. We performed a preliminary evaluation of a new low-flow sidestream capnography technology (Microstream), to determine its accuracy by measuring the end-tidal-arterial CO_2 (PetCO_2 – PaCO_2) gradient in newborns with and without pulmonary disease.

Our results show that this new sidestream capnography technology measured a normal PetCO_2 – PaCO_2 gradient in newborns without pulmonary disease, and an elevated gradient in newborns with pulmonary conditions. There was a significant difference in the PetCO_2 – PaCO_2 gradient between the two groups of patients with and without pulmonary disease.

Mainstream and conventional sidestream capnography devices used for monitoring adults and older children underestimate alveolar CO_2 in newborns, resulting in falsely low PetCO_2 readings.^{7–12} Mainstream devices, which involve placement of an airway adapter between the proximal endotracheal tube and the ventilator circuit, increase dead space in the system and compete for tidal volume. Because the tidal volumes of neonatal patients are small and respiratory rates are high, the alveolar CO_2 is diluted with dead-space gas from the ventilator circuit. Early studies of mainstream capnography in newborns were not encouraging, and even reported elevations of PaCO_2 due to rebreathing in the presence of the airway adapter.²¹ McEvedy et al.²² also demonstrated that use of a mainstream capnography sensor increased transcutaneous PCO_2 during a study of intubated newborns. In a study of anesthetized infants, Rich et al.²³ compared PetCO_2 measurements taken directly from the proximal aspect of the endotracheal tube with values recorded from a mainstream capnography device. They found that direct measurements taken from the proximal endotracheal tube were significantly closer to arterial CO_2 than values obtained from the capnograph.²³

Mainstream devices with dead space volumes of <1 ml have recently been developed and studied. Rozycki et al.²⁴ described mainstream capnography performed on 45 neonatal patients, including eight patients with birth weights <1000 g. The correlation coefficient between PetCO_2 and PaCO_2 was 0.833, and capnography underestimated arterial CO_2 by a bias of approximately 7 mm Hg (95% CI, ± 11.5 mm Hg). Of note, the results were similar in the ELBW infants, and the severity of lung disease had only a small influence on the degree of bias.²⁴ PetCO_2 and PaCO_2 values were compared but waveform data were not recorded in this study.

Sidestream capnography is performed by continuously sampling exhaled gas from a side port on the proximal endotracheal tube. The volume of gas siphoned from the breathing circuit is determined by the capnograph's characteristics. The advantage of sidestream devices is that exhaled gas is sampled before entry into the breathing circuit, thus reducing dilution with dead space gas. However, conventional sidestream capnographs require a large sample cell and, therefore, a high flow rate (150–200 ml/min) because the infrared source is not

specific for the wavelength of carbon dioxide.¹⁶ For the neonate with high respiratory rates and low tidal volumes, this rate of gas withdrawal results in entrainment of dead space gas from the breathing circuit and dilution of alveolar CO_2 . Additionally, incomplete flushing of the large sample cell by the neonate's relatively small breath packets further dilutes PetCO_2 . This was demonstrated by Badgwell et al.²⁵ who studied anesthetized, intubated infants and children without cardiopulmonary disease. PetCO_2 was measured using a long sampling catheter at the distal end of the endotracheal tube, and was better correlated with PaCO_2 compared to PetCO_2 measured *via* a sidestream adapter at the proximal aspect.²⁵

Microstream capnography employs a sampling flow rate of 50 ml/min, approximately one third that used by previously studied conventional sidestream systems. This low flow rate eliminates the competition for tidal volume and also decreases condensation within the system. Because of the highly CO_2 -specific infrared source (emission that exactly matches the absorption spectrum of the CO_2 molecule), the sample cell utilizes a much smaller volume (15 μl) that permits a low flow rate without compromising response rate or accuracy. These features preserve accuracy by preventing the mixing of the small inspiratory and expiratory volumes observed in newborns, while rapid response time is maintained by laminar gas flow throughout the breathing circuit.¹⁶

Adult capnogram waveforms are characterized by a triphasic shape that has been described in both normal and disease states (Figure 1).^{11,13} The ascending phase (Phase I) represents the process of alveolar gas mixing with dead space gas during initial expiration. The alveolar plateau (Phase II) represents progressive emptying of lung units over time. The descending phase (Phase III) correlates with the inspiratory Phase. Waveform analysis of adult asthmatic patients has demonstrated several parameters that correlate with spirometric measures of pulmonary function, including Forced expiratory volume in 1 second (FEV_1) and Peak expiratory flow rate (PEFR).^{14,15} Alpha angle, alveolar plateau slope,

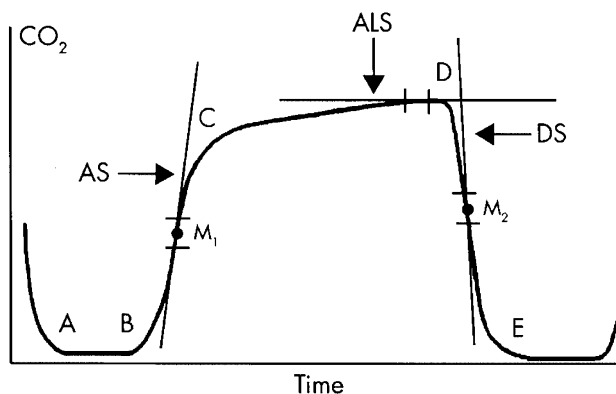


Figure 1. A normal adult capnogram with superimposed waveform parameters. Phase I=points B to C (ascending phase), Phase II=points C to D (alveolar plateau), Phase III=points D to E (descending phase). AS=ascending slope, DS=descending slope, ALS=alveolar slope, M_1 =midpoint between B and C, M_2 =midpoint between D and E.

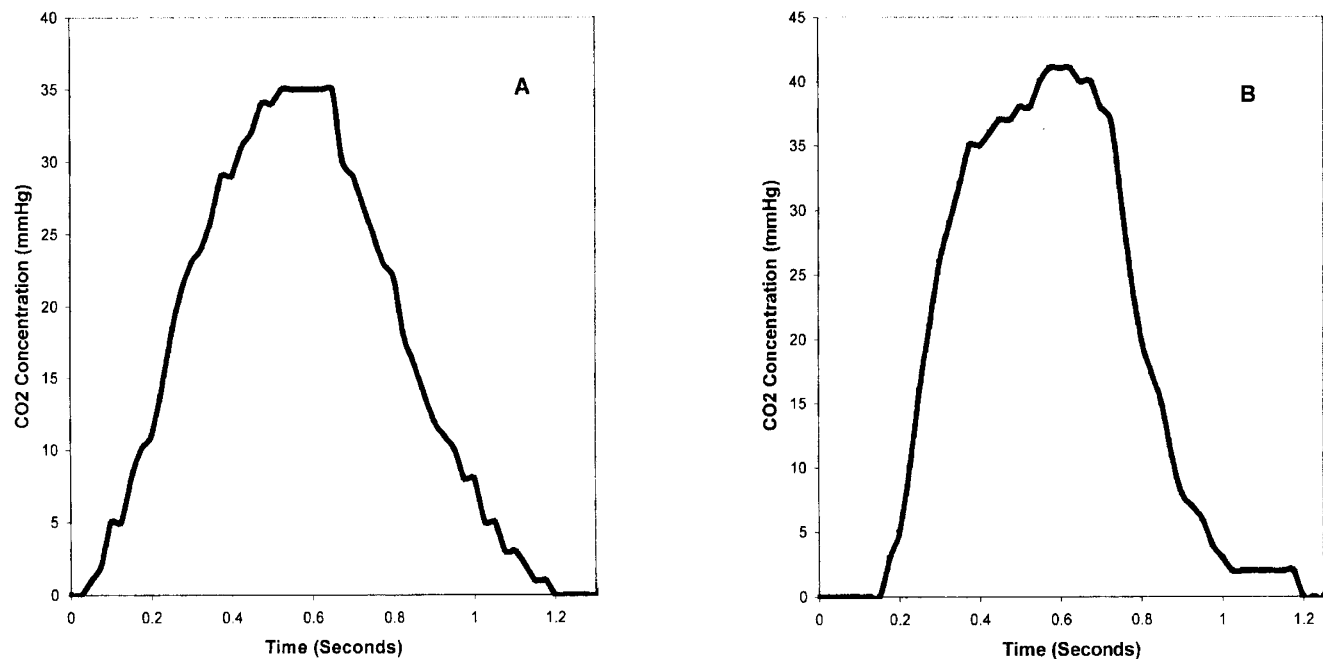


Figure 2. **A**, A sample recorded waveform from a newborn without pulmonary disease. Note the qualitative difference in the Phase II segment of this capnogram when compared to that of a normal adult capnogram seen in Figure 1. **B**, A sample recorded waveform from a newborn with pulmonary disease. Note the more rapid ascent and descent in Phases I and III, respectively when compared to (**A**).

and area ratios can be used clinically for estimating the severity of bronchospasm and airway obstruction in adults.

We analyzed capnograms from our subjects, and determined that the rapid respiratory rate and low tidal volumes of newborn infants significantly alter the characteristic waveform (Figure 2, *A* and *B*). We noted that alveolar plateau slope and area ratio were respiratory rate-dependent variables with significant inpatient variability in our study population. We then looked for waveform parameters that were respiratory rate-independent and without significant inpatient variability. Our data demonstrated differences between the pulmonary disease group and controls for six waveform parameters: ascending angle and slope, alpha angle, descending angle and slope, and alveolar angle. There were no significant differences between the pulmonary disease subgroups for any of the waveform parameters. Stepwise logistic regression identified four multivariate predictors that independently differentiated patients with pulmonary disease from controls: ascending slope, alveolar angle, alpha angle, and descending angle.

The ascending slope and angle represent Phase I of the capnogram, which is altered by diseases in which ventilation-perfusion (V/Q) mismatching occurs. Our analysis demonstrated a significant increase in the ascending slope and angle when comparing infants receiving mechanical ventilation, with underlying pulmonary disease to those without lung disease. As the alpha angle is a function of ascending angle and alveolar angle, as described in the Methods section, diseases that alter Phases I and II of the capnogram will also impact the alpha angle. In particular, diseases that increase the ascending angle relative to alveolar angle will decrease the alpha angle. Our data demonstrate a significantly

smaller alpha angle between infants with and without pulmonary disease. This is consistent with the Phase I capnogram of mechanically ventilated infants with RDS or MAS/PPHN being steeper than that of control infants and may be explained by the decreased lung compliance seen in RDS. During the initial expiratory phase, more rapid lung recoil would result in a steeper slope to the ascending phase of the capnogram. Although, MAS/PPHN may represent heterogeneous pulmonary pathology, all infants with MAS/PPHN in our study had radiographic evidence of diffuse interstitial lung disease without significant areas of air trapping/hyperinflation. These findings suggest that the primary pathophysiologic process was impaired compliance as opposed to decreased dead space ventilation consistent with recent data that acquired surfactant deficiency or dysfunction plays a significant role in these patients.²⁶

The descending slope and angle of the capnogram represent the inspiratory phase of ventilation, known as Phase III. We found a significant increase in the descending slope and angle when comparing mechanically ventilated newborns with and without lung disease. This may be explained by the fact that in the presence of impaired lung compliance, alveolar units have shorter time constants and, therefore, more rapid displacement of carbon dioxide during inspiration. (Table 4).

This study is limited by its small sample size and by the heterogeneity of the population studied, including gestational age, birth weight, postnatal age, and type of lung disease. Further study to examine how these described waveform parameters change with pulmonary disease severity and in response to therapies is needed and may allow for the clinical application of this technology in the NICU. This application of continuous CO₂ monitoring in infants with

Table 4

Capnogram phase	Breath cycle phase	Physiologic effectors
I	early exhalation	airway resistance lung recoil
II	late exhalation	positive pressure ventilation airway resistance breath rate I:E ratio
III	inhalation	pulmonary compliance positive pressure ventilation

pulmonary disease would be a welcomed modality given the previously discussed deleterious affects of hypo- and hypercapnea in the newborn. Currently, newer generations of exogenous surfactants are reporting more rapid response times, thereby making continuous monitoring of the ventilatory status in newborns increasingly important.^{27,28}

CONCLUSION

Our study is the first to demonstrate a sidestream capnography technology that can accurately estimate PaCO₂ in intubated neonatal patients. In the population without lung disease and a normal alveolar–arterial CO₂ gradient, PetCO₂–PaCO₂ gradients were within normal limits. In a heterogeneous population of neonates with lung disease, PetCO₂–PaCO₂ gradients were abnormal. We also identified four waveform parameters that may be useful in distinguishing in future studies between mechanically ventilated newborn patients with and without lung disease.

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