***In Vitro* Validation and Clinical Testing of an Indirect Calorimetry System for Ventilated Preterm Infants That Is Unaffected by Endotracheal Tube Leaks and Can Be Used during Nasal Continuous Positive Airway Pressure**

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ABSTRACT

Energy expenditure measurements in ventilated preterm infants are difficult because indirect calorimetry underestimates energy expenditure during gas leaks around uncuffed endotracheal tubes routinely used in preterm infants or during nasal continuous positive airway pressure (CPAP). We, therefore, developed a breath collector that simultaneously sampled expired air expelled at the ventilator outlet and escaping via the tube leak from the infant's mouth and nose. Our breath collector was combined with a proprietary calorimeter (Deltatrac II). *In vitro* validation was done by methanol burning (Vo_2 , 13.8 mL/min; Vco_2 , 9.2 mL/min) during intermittent positive pressure ventilation (IPPV) with two commonly used ventilators (Sechrist IV-100B and Infant Star). Measurement error was determined at different ventilator flows, peak inspiratory pressures of 12–24 cm H_2O , and during a complete tube leak. The mean measurement error with both ventilators was low ($\text{Vo}_2 \pm 3\%$, $\text{Vco}_2 \pm 2\%$) even during a complete tube leak and did not increase with peak inspiratory pressure. The system response time was 2 min. *In*

vivo measurements at the bedside were performed in 25 preterm infants (body weight, 537–1402 g). Energy expenditure during IPPV was 40 ± 9 kcal/kg per day and 46 ± 15 kcal/kg per day during nasal CPAP. The tube leak in the preterm infants studied during IPPV was 0 to 47%, and during nasal CPAP 84 to 97%. In conclusion, indirect calorimetry performed with our breath collector was accurate during IPPV and nasal CPAP and was unaffected by tube leaks. (*Pediatr Res* 49: 394–401, 2001)

Abbreviations

CPAP, continuous positive airway pressure
EE, energy expenditure
Fio₂, fraction of inspiratory oxygen
PEEP, positive endexpiratory pressure
PIP, peak inspiratory pressure
RQ, respiratory quotient
Vco₂, carbon dioxide production
Vo₂, oxygen consumption

Nutritional intake has to meet energy requirements. Although the EE of spontaneously breathing growing preterm infants is well documented (1, 2), there is a great need for EE measurements in critically ill and ventilated preterm infants (3). These infants can have large variations in EE due to the underlying disease, surgery, therapeutic interventions, or medication. The reason for the paucity of data is the methodologic difficulties for indirect calorimetry in ventilated preterm infants. The routine use of uncuffed endotracheal tubes leads to unpredictable leakage of expired air through mouth and nose (tube leak) in up to 50% of ventilated neonates (4), and the

commonly used nasal CPAP represents a maximal tube leak. In previous measurements of EE, many ventilated preterm infants with tube leaks had to be excluded from analysis (5, 6), and no measurements during nasal CPAP have been reported.

We, therefore, developed an indirect calorimetry system with the following capabilities: 1) accurate measurements in intubated preterm infants regardless of tube leak, 2) accurate measurements during nasal CPAP, 3) applicable in combination with pressure-controlled constant-flow ventilators, 4) applicable during increased Fio₂, 5) accurate measurements of low absolute values of Vo₂ and Vco₂, and 6) easy to use at the bedside without undue disturbance of the patient.

The purpose of the present study was to validate this calorimetry system *in vitro* and to evaluate its performance in the clinical setting.

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METHODS

The Breath Collector

We built a breath collector that simultaneously sampled expired air expelled from the ventilator and coming from the infant's mouth and nose (Fig. 1). The breath collector was made from a 200-mL plastic container (Sarstedt, Nürnberg, Germany). Air from the infant's mouth and nose entered through the open container bottom ($\varnothing$ 4 cm). A small indentation in the lower sidewall was for the endotracheal tube. In the container lid was an opening with a tube leading to the calorimeter.

Figure 1. Use of the breath collector in combination with ventilator A. (Top) Schematic drawing of the measurement setup. Thin arrows represent flow of exhaled gas escaping via the tube leak; gray arrows represent exhaled gas from the endotracheal tube. (Bottom) Measurement in a preterm infant.

Calorimeter

We used the breath collector together with the commercially available indirect calorimeter Deltatrac II (Datex Division Instrumentarium Corp., Helsinki, Finland). A constant-flow generator in the calorimeter withdraws the expired air diluted with room air from the breath collector. The flow rate is independent of the added flux of room air. CO_2 and VO_2 are calculated from the constant flow of the diluted expired air and the concentration differences between diluted expired air and room air. This requires high-resolution gas sensors that can measure small concentration differences. The paramagnetic oxygen sensor and the infrared CO_2 sensor in the Deltatrac II have a high resolution of 0.01% (7). We modified the constant-flow generator to produce flow rates between 1 and 10 L/min and calibrated the flow generator by quantitative methanol burning (8).

Components of the *In Vitro* Validation System

We tested the breath collector in combination with different ventilators and at different ventilator settings with a self-made *in vitro* validation system. It consisted of an EE simulation by quantitative methanol burning, a test lung, and the breath collector/calorimeter (Fig. 2). We simulated EE with a miniburner previously built to validate indirect calorimetry in spontaneously breathing infants (8). In short, methanol (methanol extra pure >99.5%; Merck, Darmstadt, Germany) delivered by a precision infusion pump (Perfusor fm; Braun-Melsungen AG, Melsungen, Germany) at a rate of 1 mL/min was burned at the tip of a glass capillary, producing a VCO_2 of 9.2 mL/min and a VO_2 of 13.8 mL/min (= EE of 0.16 kcal/min or 0.69 kJ/min). These VO_2 and VCO_2 values are in the range expected in an infant of approximately 2 kg body weight. Methanol burning was done inside a small airtight box incorporated in the ventilator circuit. We used a plastic test lung with a volume of 40 mL (Draeger AG, Lübeck, Germany).

Protocol for the *In Vitro* Experiments

We tested the breath collector in combination with two pressure-controlled constant-flow ventilators for preterm infants, the Sechrist IV-100B (Sechrist Industries, Anaheim, CA, U.S.A.) (ventilator A) and the Infant Star software version 83 (Nellcor Puritan Bennet Inc., Carlsbad, CA, U.S.A.) (ventilator B). When used with ventilator A, the expiratory valve located at the end of the ventilator circuit was placed inside the breath collector with the gas outlets of the valve pointing toward the calorimeter to facilitate gas sampling (Fig. 2A). In ventilator B, the expiratory valve is mounted on the ventilator. We sealed this expiratory block with adhesive tape to prevent any gas leakage and directed the gas flow from the valve via a plastic tube to the breath collector (Fig. 2B).

First, the gas analyzers were calibrated with a known gas mixture (5% CO_2 and 95% O_2 , Datex Division Instrumentarium Corp., Helsinki, Finland), and the calorimeter flow was set to 6 L/min. Then the ventilator was switched on, the methanol flame in the ventilator circuit was lit, and the burning chamber was closed airtight. All experiments were done in room air

Figure 2. Schematic drawing of the *in vitro* validation setup with ventilator A (A), ventilator B (B), and during simulation of a complete tube leak (C). Arrows indicate the direction of gas flow in the ventilator circuits.

because of the danger of explosion during combustions at raised F_{IO_2} . Gases from the ventilator passed through the burning chamber and test lung to the breath collector that was held several millimeters above a flat surface by a research assistant to mimic the application in an infant. To avoid contaminations by expired air from the research assistant, he stayed at least 30 cm away from the breath collector during measurements.

We determined the measurement error for the combination with each ventilator at ventilator settings commonly used for preterm infants, *i.e.* PIP up to 24 cm H_2O , a PEEP of 3 cm H_2O , and a rate of 60/min. For each experimental condition, we performed five separate measurements. The actual measurement, lasting 20 min, followed 10 min of equilibration. The measurement error was calculated as

$$\text{measurement error} = \frac{\text{observed value} - \text{expected value}}{\text{expected value}} \times 100 \quad (1)$$

Determination of measurement error at different ventilator flows. We determined the measurement error at a calorimeter flow of 6 L/min at constant ventilator flows of 3, 4, 5, and 6 L/min. The other ventilator settings were kept constant (rate, 60/min; PEEP, 3 cm H_2O ; PIP, 15 cm H_2O).

Determination of measurement error at different PIP. We changed PIP from 12 to 24 cm H_2O . The other ventilator settings were kept constant (rate, 60/min; PEEP, 3 cm H_2O ; flow, 4 L/min).

Determination of measurement error with a simulated complete tube leak. To simulate a complete tube leak, *i.e.* all expired air comes out of the ventilated infant's mouth and nose, the methanol burner was placed inside a manikin the size of a preterm infant with the methanol flame burning at the position of the manikin's mouth. The manikin is described in detail elsewhere (8). Gas was sampled by holding the breath collector with the bottom opening above the manikin's face while mechanical ventilation was simulated at a rate of 60/min, PIP of 15 cm H_2O , PEEP of 3 cm H_2O (Fig. 2C).

Measurement of response time. The response time of the system was tested by measuring the time interval between a

step change in methanol combustion rate from 1.0 to 1.1 mL/min (= increase of V_{CO_2} from 9.2 to 10.1 mL/min) and the accurate and stable measurement of the increased V_{CO_2} .

Clinical Testing

We measured VO_2 and V_{CO_2} in mechanically ventilated preterm infants and infants receiving nasal CPAP. To expose our system to a variety of clinical situations, we studied patients of different sizes, postnatal ages, and intensity of mechanical ventilation. Exclusion criteria were the following: 1) no parental consent, 2) unstable mechanical ventilation, 3) birth weight <500 g, 4) PIP >25 cm H_2O , 5) F_{IO_2} >0.6 L/L. All infants were in incubators (model 8000, Draeger AG, Lübeck, Germany) at thermoneutral temperature. Constant flow at the ventilators was 4 L/min; the internal calorimeter flow was 6 L/min. Nasal CPAP was provided via a shortened endotracheal tube placed in the epipharynx.

The present study was approved by the Institutional Review Board of the hospital, and written parental consent was obtained.

Measurement Protocol for Mechanically Ventilated Infants and Infants on Nasal CPAP

After the infant had received nursing care and gavage feeding, he was positioned supine and the breath collector was connected to the ventilator circuit. The breath collector was easy to connect to the ventilator circuits. This required a short disconnection of the expiratory valve of ventilator A for one or two breaths. No disconnection was necessary when the breath collector was used with ventilator B. Measurements started after an equilibration period of 10 min.

Measurement of tube leak. To measure the tube leak, the breath collector was placed beside the infant's head for 30 min so that the air escaping through mouth and nose was no longer collected. The tube leak was calculated from the difference in V_{CO_2} measurements with and without collecting gas from the infant's mouth and nose.

Measurement of VO_2 and V_{CO_2} . To simultaneously collect expired air from the ventilator valve and from the tube leak, the

breath collector was held several millimeters above the infant's mouth and nose by a research assistant without actually touching the infant. When the infant turned the head, the research assistant repositioned the breath collector to keep it in front of mouth and nose (Fig. 1).

In infants on nasal CPAP breathing room air, V_{CO_2} and VO_2 were continuously measured for 120 min.

In endotracheally intubated infants with a raised F_{IO_2} , V_{CO_2} was measured continuously for 90 min. The VO_2 could not be measured due to the dilution with room air. Instead, we measured the RQ for 30 min. The RQ, the V_{CO_2}/VO_2 ratio, is unaffected by partial loss of expired air and is accurate in raised F_{IO_2} as long as no room air dilutes the collected gas. For the duration of the RQ measurement, therefore, we reduced the calorimeter flow to 1 L/min at an unchanged ventilator flow of 4 L/min. Thus, much more gas entered the breath collector than was withdrawn. This spillover prevented the dilution of the collected gas by room air. As an additional precaution against dilution by room air, the breath collector was wrapped in a thin polyethylene foil. During RQ measurements, oxygen was taken from a gas tank instead of the wall source to minimize F_{IO_2} fluctuations.

In infants on nasal CPAP in raised F_{IO_2} , only V_{CO_2} was measured because the amount of expired air from the expiratory valve was insufficient to measure the RQ.

Transcutaneous P_{CO_2} and heart rate were measured continuously, and the infant's activity was scored every minute by the research assistant using a modified Brueck score (9). Time spent in sleep was defined as the time with a Brueck score of -3 (eyes closed, only facial movements) or -4 (eyes closed, no movements).

Calculations

VO_2 (mL/min), V_{CO_2} (mL/min), and RQ were calculated from the O_2 and CO_2 concentrations measured in the inspiratory gas (F_{IO_2} and F_{ICO_2}) and in the diluted expiratory gas passing through the calorimeter (F_{EO_2} and F_{ECO_2}) and the constant internal calorimeter flow (Q ; mL/min) by using the Haldane transformation (Equations 2–4) (10). In infants with raised F_{IO_2} , we measured V_{CO_2} and RQ and calculated VO_2 according to Equation 5.

$$V_{CO_2} = (F_{ECO_2} - F_{ICO_2}) \times Q \quad (2)$$

$$RQ = \frac{1 - F_{IO_2}}{[(F_{IO_2} - F_{EO_2})/F_{ECO_2}] - F_{IO_2}} \quad (3)$$

$$VO_2 = \frac{(F_{IO_2} - F_{EO_2}) - F_{IO_2} \times F_{ECO_2}}{1 - F_{IO_2}} \times Q \quad (4)$$

$$VO_2 = RQ/V_{CO_2} \quad (5)$$

EE (kcal/d) was calculated from VO_2 , V_{CO_2} , and urinary nitrogen excretion (Un) that was estimated as 0.15 g N per

kg body weight (11).

$$EE = 5.5 \times VO_2 + 1.76 \times V_{CO_2} - 1.99 \times Un \quad (6)$$

Statistical Analysis

Data were analyzed with the SPSS statistical software (SPSS Inc., Chicago, IL, U.S.A.). Normally distributed data are presented as mean $\pm$ SD, not normally distributed data as median (range).

RESULTS

In Vitro Experiments

Determination of measurement error at different ventilator flows. As long as the calorimeter flow was higher than the flow at the ventilator, gas from the methanol burn was completely sampled and VO_2 and V_{CO_2} measurements were sufficiently close to the predicted values to be clinically acceptable (Fig. 3). The measurement error was small at a ventilator flow of 4 L/min and a calorimeter flow of 6 L/min in both ventilator types [ventilator A, $1 \pm 1\%$ (V_{CO_2}) and $-1 \pm 5\%$ (VO_2); ventilator B, $3 \pm 2\%$ (V_{CO_2}) and $-2 \pm 1\%$ (VO_2)]. Therefore, this flow combination was used in all subsequent experiments.

Determination of measurement error at different PIP. Changing PIP between 12 and 24 cm H_2O did not influence the VO_2 and V_{CO_2} measurement error with both ventilators (Table 1).

Determination of measurement error with a simulated complete tube leak. When methanol was burned with the manikin simulating a complete tube leak during mechanical ventilation, measurement error with ventilator A was $1 \pm 4\%$ (V_{CO_2}) and $0.3 \pm 4\%$ (VO_2), and measurement error with ventilator B was $1 \pm 2\%$ (V_{CO_2}) and $-0.5 \pm 3\%$ (VO_2).

Measurement of the response time. The response time of the system to a step change in methanol burn was 2 min (Fig. 4).

Figure 3. Measurement error for VO_2 (open squares) and V_{CO_2} (closed squares) at different ventilator flow rates (ventilator A) during quantitative methanol burning. The calorimeter flow rate was 6 L/min. Data are mean $\pm$ SD of five methanol burns.

Table 1. V_{CO_2} and Vo_2 measurement error at different PIP with ventilator A and ventilator B

PIP	V_{CO_2} measurement error (%)		Vo_2 measurement error (%)	
	ventilator A	ventilator B	ventilator A	ventilator B
12 cm H ₂ O	1 ± 1	1 ± 4	-1 ± 5	2 ± 5
20 cm H ₂ O	0 ± 2	0 ± 2	-2 ± 5	-2 ± 1
24 cm H ₂ O	-1 ± 1	n.d.	-2 ± 4	n.d.

n.d., not done. Values are mean ± SD of five experiments each.

Figure 4. Response time of the system. A step change in V_{CO_2} from 9.2 to 10.1 mL/min was produced by increasing methanol delivery rate. Data (triangles) are mean ± SD of five methanol burns.

Clinical Testing

We studied 15 preterm infants during intermittent positive pressure ventilation and 10 preterm infants during nasal CPAP (ventilator A) (Table 2). The infants were not disturbed by the measurement and were sleeping most (median ≥ 85%) of the observation period.

Measurement of tube leak. The tube leaks in the intubated preterm infants varied considerably from 0 to 47% (Table 3). Tube-leak size was independent of PIP or body weight. During nasal CPAP, most of the expired air escaped via nose and mouth, and the tube leak ranged from 84 to 97%.

Measurement of V_{CO_2} and Vo_2 . For these measurements, air escaping from the expiratory valve and via mouth and nose were sampled simultaneously and the values are, therefore, undiminished by tube leaks (Table 4). V_{CO_2} was measured in all infants. Transcutaneously measured P_{CO_2} (Tcp_{CO_2}) was not different at start and end of the measurements, indicating that

no CO_2 retention had occurred. Vo_2 was measured in seven infants on nasal CPAP breathing room air. Vo_2 was calculated from V_{CO_2} and RQ in all endotracheally intubated preterm infants with raised F_{IO_2} . In three infants on nasal CPAP at raised F_{IO_2} , we could only measure V_{CO_2} .

DISCUSSION

EE measurements in critically ill ventilated neonates are needed to define energy requirements but have been impeded by methodologic problems caused by the strategies of mechanical ventilation typically used in neonates. We developed a breath collector for precise indirect calorimetry that can be used in intubated preterm infants regardless of tube leak and in preterm infants with nasal CPAP. The system is easy to use at the bedside without disturbing the infant.

The Calorimeter

We used a commercially available calorimeter producing a constant internal gas flow instead of measuring flow rates. Most important in the context of this study, a calorimeter with a constant internal gas flow allows simultaneous sampling of gas from ventilator and infant at the bedside in the same incubator that is used for clinical care without additional complicated equipment. Calorimeters using flow sensors instead of producing a constant flow have been used in mechanically ventilated preterm infants (12–14). But continuous measurements of gas flows are extremely difficult under clinical conditions (15), and a simultaneous collection of gas from ventilator and infant is not possible with these calorimeters.

When a constant-flow calorimeter is used, the dilution of expired air gets higher when the infants studied get smaller. Due to the high-resolution gas analysers we used, we could measure absolute Vo_2 or V_{CO_2} as low as 1.5 mL/min, corresponding to an infant with a body weight of 500 g at the calorimeter flow of 6 L/min. We do not recommend use of our system for infants with a body weight <500 g.

Table 2. Clinical characteristics of the preterm neonates studied

	Ventilator A IPPV	Ventilator B IPPV	Ventilator A Nasal CPAP
No.	10	5	10
Gestational age (wk)	26 (23–29)*	27 (26–28)	27 (26–29)
Birth weight (g)	783 (554–1244)	784 (733–1244)	932 (670–1475)
Postnatal age (d)	3 (1–5)	5 (1–36)	7 (1–21) 5
Actual body weight (g)	732 (537–1280)	750 (691–1134)	933 (687–1402)
Heart rate (per min)	152 (140–163)	160 (145–170)	148 (141–164)
Sleep (quiet + active) (% of total)	85 (78–91)	85 (75–94)	88 (70–92)

* median (range); IPPV indicates intermittent positive pressure ventilation.

Table 3. Tube leak in preterm neonates during IPPV with two different ventilators and during nasal CPAP

	IPPV ventilator A	IPPV ventilator B	Nasal CPAP ventilator A
No. of subjects	10	5	10
F _i O ₂ (L/L)	0.37 (0.25–0.60)*	0.34 (0.30–0.50)	0.21 (0.21–0.42)
PEEP (cm H ₂ O)	3 (2–4)	3 (3–4)	3 (3–4)
PIP (cm H ₂ O)	14 (10–22)	14 (11–20)	
Ventilator rate (/min)	69 (38–79)	60 (30–69)	
Tube leak (%)	26 (4–47)	5 (0–31)	90 (84–97)

Tube leak was calculated from the difference in Vco₂ measurements with and without collecting gas from the infant's mouth and nose.

* median (range).

Table 4. Vco₂, Vo₂, and EE in preterm neonates during IPPV with two different ventilators and during nasal CPAP

	IPPV ventilator A	IPPV ventilator B	Nasal CPAP ventilator A
No. of subjects	10	5	10
Vco ₂ (mL/kg per min)	4.8 ± 0.9§	5.8 ± 1.3	5.2 ± 1.8
Tcpco ₂ start (mm Hg)	49 (38–65)*	44 (39–59)	51 (35–67)
Tcpco ₂ end (mm Hg)	51 (42–64)	40 (38–58)	49 (34–61)
RQ	0.90 ± 0.01	0.89 ± 0.02	0.89 ± 0.02+
Vo ₂ (mL/kg per min)	5.3 ± 1.0	6.5 ± 1.5	6.6 ± 2.2+
EE (kcal/kg per day)	37 ± 7	46 ± 11	41 ± 15+

For these measurements, expired air escaping from the expiratory valve and via mouth and nose was sampled simultaneously and the measurements are, therefore, not affected by tube leaks. Transcutaneously measured Pco₂ (Tcpco₂) was not different at start and end of the measurements.

§ mean ± SD.

* median (range).

+ seven preterm infants on nasal CPAP in room air.

Validation during Intermittent Positive Pressure Ventilation

A calorimetry system for ventilated preterm infants should be compatible with constant-flow pressure-controlled ventilators because these are routinely used in preterm infants. We validated our breath collector *in vitro* in combination with two mechanical ventilators for neonates.

If one uses the Deltatrac indirect calorimeter as was used in this study or another metabolic cart with a constant flow, the flow to the calorimeter must be higher than the flow from the ventilator to ensure that no expired air is lost. We demonstrated that gas sampling with our collector was complete with a calorimeter flow of 6 L/min and a ventilator flow of 4 L/min, which was the minimal flow required to reach PIP up to 30 cm H₂O during short inspiratory times (0.3 s). In a previous animal study, gas sampling was complete when the internal constant flow of the calorimeter was at least 10% higher than the ventilator flow (16). Lucas *et al.* (17) achieved accurate measurements of Vco₂ in preterm infants by adjusting calorimeter flow approximately 25% higher than ventilator flow.

Our measurements with the breath collector were accurate independent of the PIP. We could not test pressures >24 cm H₂O *in vitro* because then pressure impeded methanol burning.

The response time of our system to a step change in methanol delivery was only 2 min because the breath collector had a volume of only 200 mL. Lucas *et al.* (17) used a 6–8-L plastic bag to collect the gases expelled from the ventilator but did not report the response time.

Our breath collector should also be compatible with volume-controlled ventilators, though we did not validate this. When indirect calorimetry is performed in ventilated infants, the type

of ventilator and the type of calorimeter used should be reported together with detailed validation data for this combination of instruments.

The Tube Leak

A calorimetry system for ventilated preterm infants should capture the expired gases bypassing the endotracheal tube (tube leak). Tube leaks occur frequently in preterm infants (4, 14) because uncuffed endotracheal tubes are routinely used and result in an underestimation of Vo₂ and Vco₂.

Our collector simultaneously and continuously collected air escaping via the tube leak through the infant's mouth and nose and air coming out of the expiratory valve of the ventilator. Thus, the expired air was always sampled completely, regardless of the size of the tube leak and even when a complete tube leak was simulated. Simultaneous sampling of air from the ventilator and from the patient's mouth and nose has been described by Selby *et al.* (18) for ventilated children using a large hood, but they did not provide *in vitro* validation data. In our clinical measurements, we frequently detected tube leaks, and they were highly variable between infants.

Other methods proposed to correct for the tube leak have relevant drawbacks. In research settings, the tube leak was determined by directly measuring the infant's inspired and expired flow rates (14, 16), by measuring CO₂ over the infant's face by infrared capnometry (4, 10), or by using double-circuit calorimetry (19). These methods require use of additional pneumotachographs, lung function monitors, or CO₂ analyzers and complicate the measurement setup and data analysis. Measuring the tube leak only at the beginning and end of the actual measurement (13, 17) cannot provide continuous data

for the total measurement period. If all infants with audible air leaks were excluded from analysis as was done in clinical studies of EE (5, 20), up to 50% of otherwise eligible infants could not be studied (21) and, even without an audible tube leak, up to 8% of exhaled breath bypassed the uncuffed endotracheal tube (14).

Nasal CPAP

A calorimetry system for ventilated preterm infants should be able to measure infants on nasal CPAP, because this ventilatory support is frequently and increasingly used in preterm infants (22, 23). Nasal CPAP produced a maximal tube leak, but still up to 16% of the expired air came from the ventilator outlet. Thus, only a system that continuously and simultaneously samples air from the infant's mouth and nose and from the ventilator, like our collector, can be used in preterm infants on nasal CPAP.

Measurements in Increased F_{IO_2}

A calorimetry system for ventilated preterm infants should be able to measure EE in infants requiring increased F_{IO_2} . We did not perform an *in vitro* validation of our system in increased F_{IO_2} because of the risk of methanol explosion. Yet, the calorimeter we used has been extensively validated *in vitro* in raised F_{IO_2} (6, 24, 25), and accuracy was acceptable up to an F_{IO_2} of 0.6. With a calorimeter producing a constant internal flow, continuous VO_2 measurements at raised F_{IO_2} require considerable technical effort (19). Therefore, instead of measuring VO_2 directly, we calculated VO_2 from the continuously measured V_{CO_2} and a short-term RQ measurement (18) in intubated preterm infants at raised F_{IO_2} , with the assumption that no relevant RQ changes occurred during the total measurement period. The RQ measurement required reducing the calorimeter flow and connecting the respirator to an oxygen tank because this minimizes F_{IO_2} fluctuations (14) that disturb the measurements (26).

During nasal CPAP at raised F_{IO_2} , we could only measure V_{CO_2} . EE can be calculated from V_{CO_2} with a fixed RQ estimate (26) or an RQ estimation from nutritional intake (27). Both RQ estimates have been used in preterm infants to calculate EE from V_{CO_2} measured by the different disappearance rates of stable water isotopes (doubly labeled water method) (28, 29).

Use in the Clinical Setting

A calorimetry system for ventilated preterm infants should be easy to use and should not irritate the patient. Our calorimetry system can be used at the bedside in the intensive care unit and does not require transfer of the infant to a metabolic laboratory or to a research incubator. Connecting the breath collector to the ventilator required no or only a short disconnection of the ventilator circuit. We used the system only with nasotracheally intubated infants, but it can also be used with orotracheal tubes.

We have previously shown that the collection of exhaled gas with a sampling device held close to the infant's face but

without actually touching it does not result in increased unrest or changes in body temperature (8). During the present measurements, the infants were sleeping 85% of the time.

A handheld device like ours requires the continuous presence of a research assistant at the bedside. Measurements over 4–6 h, necessary to extrapolate to a 24-h EE, are possible with a handheld device but no continuous measurements over 24 h. Using a hood is no alternative in very-low-birth-weight infants because for accurate sampling of expired air, high flows through the hood are necessary that lead to excessive dilution of expired air (8).

In conclusion, we have validated a breath collector *in vitro* and have shown its practicability for measurements of EE in ventilated preterm infants. The simultaneous sampling of gas coming from the ventilator and from the infant's nose and mouth allows precise measurements regardless of tube leak and during nasal CPAP. Therefore, our system improves the use of indirect calorimetry in ventilated preterm infants and provides an accurate tool for research in energy metabolism in these critically ill patients.

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