A Device for the Quantification of Oxygen Consumption and Caloric Expenditure in the Neonatal Range

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BACKGROUND: The accurate measurement of oxygen consumption (VO₂) and energy expenditure (EE) may be helpful to optimize the treatment of critically ill patients. However, current techniques are limited in their ability to accurately quantify these end points in infants due to a low VO₂, low tidal volume, and rapid respiratory rate. This study describes and validates a new device intended to perform in this size range.

METHODS: We created a customized device that quantifies inspiratory volume using a pneumotachometer and concentrations of oxygen and carbon dioxide gas in the inspiratory and expiratory limbs. We created a customized algorithm to achieve precise time alignment of these measures, incorporating bias flow and compliance factors. The device was validated in 3 ways. First, we infused a certified gas mixture (50% oxygen/50% carbon dioxide) into an artificial lung circuit, comparing measured with simulated VO₂ and carbon dioxide production (VCO₂) within a matrix of varying tidal volume (4–20 mL), respiratory rate (20–80 bpm), and fraction of inspired oxygen (0.21–0.8). Second, VO₂, VCO₂, and EE were measured in Sprague Dawley rats under mechanical ventilation and were compared to simultaneous Douglas bag collections. Third, the device was studied on n = 14 intubated, spontaneously breathing neonates and infants, comparing measured values to Douglas measurements. In all cases, we assessed for difference between the device and reference standard by linear regression and Bland–Altman analysis.

RESULTS: In vitro, the mean ± standard deviation difference between the measured and reference standard VO₂ was +0.04 ± 1.10 (95% limits of agreement, −2.11 to +2.20) mL/min and VCO₂ was +0.26 ± 0.31 (−0.36 to +0.89) mL/min; differences were similar at each respiratory rate and tidal volume measured, but higher at fraction of inspired oxygen of 0.8 than at 0.7 or lower. In rodents, the mean difference was −0.20 ± 0.55 (−1.28 to +0.89) mL/min for VO₂, +0.16 ± 0.25 (−0.32 to +0.65) mL/min for VCO₂, and −0.84 ± 3.29 (−7.30 to +5.61) kcal/d for EE. In infants, the mean VO₂ was 9.0 ± 2.5 mL/kg/min by Douglas method and was accurately measured by the device (bias, +0.22 ± 0.87 [−1.49 to +1.93] mL/kg/min). The average VCO₂ was 8.1 ± 2.3 mL/kg/min, and the device exhibited a bias of +0.33 ± 0.82 (−1.27 to +1.94) mL/kg/min. Mean bias was +2.56% ± 11.60% of the reading for VO₂ and +4.25% ± 11.20% of the reading for VCO₂; among 56 replicates, 6 measurements fell outside of the 20% error range, and no patient had >1 of 4 replicates with a >20% error in either VO₂ or VCO₂.

CONCLUSIONS: This device can measure VO₂, VCO₂, and EE with sufficient accuracy for clinical decision-making within the neonatal and pediatric size range, including in the setting of tachypnea or hyperoxia. (Anesth Analg 2018;127:95–104)

KEY POINTS

• Question: Does a device that measures inspiratory flow, and inspiratory and expiratory oxygen and carbon dioxide concentrations, accurately determine oxygen consumption, carbon dioxide production, and energy expenditure in the neonatal range?

• Findings: Device-based measures of oxygen consumption, carbon dioxide production, and energy expenditure correlate well with those simulated using a mass flow controller in vitro, and with Douglas measurements in rodents and in newborn infants.

• Meaning: This device enables the real-time analysis of oxygen consumption and energy expenditure in neonates with sufficient accuracy for clinical use.
The accurate measurement of energy expenditure (EE) and oxygen consumption (VO₂) may provide useful information for the treatment of critically ill infants and children. To date, no devices are available for the continuous, accurate quantification of these parameters in the neonatal population.

It is well established that providing adequate nutrition for patients in critical condition, especially infants and small children, results in decreased mortality and overall improved outcomes. The underestimation of EE may lead to underfeeding and inadequate caloric provision, and may worsen clinical outcomes. Alternatively, overestimation of EE may lead to overfeeding, may increase carbon dioxide (CO₂) production (VCO₂), and prolong the duration of mechanical ventilation. Overestimation of EE, whether by inaccurate measurement or by the use of estimating equations, may lead to excess fluid administration in patients who are particularly fluid sensitive, such as infants after congenital heart surgery. The use of standardized equations to estimate energy requirements has been shown to correlate poorly with measured values, both under- and overestimating EE by up to 90%. Fluctuations in metabolic rate, temperature, activity level, and overall health are clearly determinants of EE that are not captured in equations. Thus, the accurate quantification of EE in ventilated neonates is highly desirable.

Like EE, VO₂ varies greatly between health and illness and may permit identification of critical illness states. An increased VO₂ (or VCO₂) may be the first signs of fever, systemic inflammatory response, seizure, or agitation in ventilated patients, permitting early clinical intervention. Alternatively, VO₂ may decrease in patients with severe low cardiac output syndrome. Further, VO₂ is a critical component of the Fick equation, and the accuracy of measurements of cardiac output and vascular resistances (critical in the treatment of infants with congenital heart disease) relies on the accurate quantification of VO₂. As with EE, small discrepancies in equation-based estimates of VO₂ can lead to important discrepancies (in either direction) in estimates of cardiac output or vascular resistance.

Over the past several decades, several devices have been developed which quantify EE and VO₂ using metabolic breath-by-breath devices. However, as discussed in detail below, the available repertoire to measure these variables with accuracy in the neonatal range is particularly limited. To address this important problem, we have created a new device focused on the quantification of EE and VO₂ in the neonatal range. Here, we describe this technique as well as its accuracy in vitro and in vivo.

**METHODS**

**Device Description**

As with all techniques, VO₂ and VCO₂ are measured through the accurate quantification of inspired and expired oxygen (O₂) and CO₂ content. As shown in Figure 1, the device measures inspiratory volume using a flowmeter (8311B Series 0–10 LPM nonheated pneumotachometer; Hans Rudolph, Shawnee, KS) attached at the inspiratory outlet of the ventilator (Servo-i; Maquet Critical Care, Solna, Sweden) and pressure differential sensor (±2 inches H₂O sensor; Measurement Specialties, Fremont, CA). Gas is sampled at a rate of 60 mL/min, carried via Nafion tubing (Perma Pure, Lakewood, NJ, which is used to dehumidify the respiratory gases) to a remote O₂ laser diode sensor (Oxigraf, CA) and infrared CO₂ sensor (Oxigraf, Sunnyvale, CA). Expired gas is collected at the ventilator exhaust and is similarly analyzed. A single set of O₂ and CO₂ sensors is used for the measurements of inspiratory and expiratory gases to minimize sensor-related error, and gas is alternated using an internal solenoid valve (X-Valve; Parker/Pneutronics, Hollis, NH). The timing algorithm is designed to measure O₂ and CO₂ concentrations on essentially the same sample of gas from the inspiratory and expiratory limbs in sequence.

**Figure 1.** Schematic of device attachments. The device quantifies inspiratory flow using a flowmeter at the inspiratory port from the ventilator, before the humidifier. Inspired gas is sampled distal to the humidifier to permit maximal mixing. Expiratory gas is sampled at the ventilator exhaust, also to maximize mixing. O₂ and CO₂ are each analyzed by single analyzers within the device, which alternately analyzes inspiratory and expiratory gases using a solenoid valve. CO₂ indicates carbon dioxide; O₂, oxygen; VO₂, oxygen consumption; ∆P, differential pressure.
VO₂ (mL/min at standard temperature and pressure dry) is calculated according to Equation 1, where F₁ is the fractional inspired and Fₑ is the fractional mixed expired concentrations of O₂ and CO₂:

\[
VO₂(\text{STPD}) = V'_{\text{tot}}(\text{ATPD}) \times \frac{273}{273+t_{\text{amb}}} \times \frac{P_B}{760} \times \frac{F₁O₂ \times (1-FₑCO₂) - FₑO₂ \times (1-FₑCO₂)}{1-FₑO₂ - FₑCO₂}
\]  \quad (1)

VCO₂ is calculated according to Equation 2 as follows:

\[
VCO₂(\text{STPD}) = V'_{\text{tot}}(\text{ATPD}) \times \frac{273}{273+t_{\text{amb}}} \times \frac{P_B}{760} \times \frac{FₑCO₂ \times (1-F₁O₂) - FₑO₂ \times (1-FₑO₂)}{1-FₑO₂ - FₑCO₂}
\]  \quad (2)

Total inspiratory gas flow \( V'_{\text{tot}} \) (L/min) in Equations 1 and 2 is measured by the pneumotach before humidification, corrected for calculated instantaneous gas viscosity based on measured fraction of inspired oxygen (FIO₂), averaged over a complete number of breaths in the measurement cycle, and determined at ambient temperature and pressure dry. The Haldane transformation is used to exclude expiratory volatilization of O₂ content in Equations 1 and 2 are measured on approximately the same physical sample of gas (traveling through the ventilatory circuit) but at different times. Because of this time delay, a complete measurement cycle lasts between 45 and 60 seconds (depending on minute ventilation), such that a single set of values (VO₂, VCO₂, and EE) is generated at this interval.

The flowmeter was linearized before each study, and calibrated daily for unidirectional measurement using a 1-L calibration syringe (Hans Rudolph, Shawnee, KS). O₂ and CO₂ sensors were calibrated using room air, O₂ (Airgas, Boston, MA), and 5% CO₂/20% O₂/balance N₂, clinical blood gas grade (accuracy 0.03% absolute; Airgas, MA).

**Device Accuracy In Vitro**

We created a lung simulator representative of the dead space and tidal volumes of neonates. This consisted of a standard neonatal ventilator circuit, humidifier (Hudson RCI; Teleflex Medical, Morrisville, NC), and artificial silicone lungs (1 or 2 NeoLung bellows; IngMar Medical, Pittsburgh, PA) to alter tidal volume and total system compliance. Mechanical ventilation took place using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden) in infant mode. We simulated metabolic gas exchange by infusing a test gas (50% CO₂ and 50% O₂ ±0.03% absolute accuracy; Scott Medical Products/Airgas, Plumsteadville, PA) into the bellows at 0–40 mL/min using a mass flow controller (MFC, MC-50SCCM; Alicat Scientific, Tucson, AZ; accuracy ±0.4% of reading, ±0.2% of full scale, factory calibrated for use with the mixture). Using this test gas, half of the infused flow rate would correspond to the VCO₂ and half of the rate would simulate a negative VO₂ (O₂ production), resulting in an expected respiratory quotient (RQ) of −1.00 independent of ventilator settings. A conversion factor of 1.092 was applied to convert from desired flow at standard temperature and pressure dry to standard cubic centimeters per minute at 25°C (used for the MFC setpoint). After a 5-minute equilibration time, measurements were taken for 20 minutes at each combination described in Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/C278 (n = 3 per combination). FIO₂ was varied between 0.21 and 0.8, respiratory rate (RR) between 20 and 80 breaths per minute, and tidal volume between 4 and 20 mL through manipulation of the ventilator settings and number of bellows. Simulated VO₂ and VCO₂ were varied between 4 and 20 mL/min through manipulation of the MFC. The resulting mixed expired CO₂ concentrations were in the range 0.5%–1.6%. Matrix design was intended to interrogate the lower limit of detection in VO₂ at the highest RR and FIO₂. Measured VO₂ and VCO₂ were compared to set MFC values by linear regression and Bland–Altman analysis. We also completed a secondary analysis intended to identify an upper limit of FIO₂ or RR beyond which the percent difference between the MFC and device reading was significantly higher (ie, the upper limits of the device). To do so, we completed a series of 1-way repeated measures analysis of variance with Dunnett multiple comparison posttests in which the percent difference between device reading in VO₂ or VCO₂ and the MFC setting was compared against FIO₂ or RR.

**Determination of Accuracy in Rodents**

The following experiments were approved by the Institutional Animal Care and Use Committee at Boston Children’s Hospital. Sprague Dawley rats (n = 12, body weight 625–780 g) underwent anesthesia using inhalational isoflurane (0.5%–2%) for placement of a transoral tracheal tube (14 g angiocatheter). Any leak around the tube was eliminated using a circumferential tracheal suture. After intubation, isoflurane was discontinued and sedation and neuromuscular blockade were provided intravenously (ketamine 40 mg/kg intraperitoneal, xylazine 5 mg/kg...
intraperitoneal, and rocuronium 2 mg/kg intravenously every 15 minutes). No inhalational anesthetics were provided for 30 minutes before or during the experimental protocol below. Mechanical ventilation (Servo-i) took place in pressure control mode using positive end-expiratory pressure 5 cm H2O, peak inspiratory pressure 20 cm H2O, and Fio2 0.4. RR was varied at either 30 or 50 bpm.

VO2, VCO2, and EE were measured by the device, a total of n = 4 times per animal. In 2 replicates, the Fio2 was provided by the ventilator as in clinical practice and the volume-averaged inspired O2 content was measured by the device. In the other 2 replicates, a certified gas mixture (40% ± 0.03% Fio2 absolute accuracy; Airgas, Boston, MA) was used as the source gas. This provided a gold standard measure of inspired O2 content for use in Douglas calculations (to determine whether the experimental mathematical coupling that takes place when the device is used to calculate inspired O2 content for Douglas collections exhibits significantly different results). In all replicates, expired O2 and CO2 content were quantified using a Douglas technique. Briefly, a 5-L non-diffusing gas collection bag (Series 6005; Hans Rudolph, Shawnee, KS) was flushed thrice with inspired gas and then expired gas from the exhaust port, followed by a timed gas collection simultaneous with device measurements. Gas volume was analyzed by calibrated 1-L syringe (Hans Rudolph, Shawnee, KS) and 60-mL disposable syringe, and O2 and CO2 using the device’s internal sensors for calculation of a reference standard VO2, VCO2, and EE. Time-averaged values for VO2, VCO2, and EE were calculated and compared to those measured simultaneously by the device using linear regression and Bland–Altman analysis. We further subanalyzed whether absolute difference in VO2 and VCO2 was different between replicates in which the Fio2 was set using the ventilator versus certified tank simultaneously with device measurements. Gas volume was analyzed by calibrated 1-L syringe (Hans Rudolph, Shawnee, KS) and 60-mL disposable syringe, and O2 and CO2 using the device’s internal sensors for calculation of a reference standard VO2, VCO2, and EE. Time-averaged values for VO2, VCO2, and EE were calculated and compared to those measured simultaneously by the device using linear regression and Bland–Altman analysis. We further subanalyzed whether absolute difference in VO2 and VCO2 was different between replicates in which the Fio2 was set using the ventilator versus certified tank simultaneously with device measurements. Gas volume was analyzed by calibrated 1-L syringe (Hans Rudolph, Shawnee, KS) and 60-mL disposable syringe, and O2 and CO2 using the device’s internal sensors for calculation of a reference standard VO2, VCO2, and EE. Time-averaged values for VO2, VCO2, and EE were calculated and compared to those measured simultaneously by the device using linear regression and Bland–Altman analysis. The absolute percent difference between device and Douglas measurements was approximately ±1 mL/min may be as useful as ±20%.

**Determination of Accuracy in Infants**

The following study was conducted after parental informed consent under a protocol approved by the institutional review board at Boston Children’s Hospital (institutional review board-P00025365) and registered on clinicaltrials.gov (registration number: NCT03154112; principal investigator name: J.N.K.; date of registration: May 12, 2017). We studied a convenience sample of neonates and infants (<6 months) who were on mechanical ventilation via a tracheal tube with a <10% leak in the cardiac or neonatal intensive care unit (ICU) (n = 14 patients). Following an identical protocol to that described in rodents, we compared device-measured VO2, VCO2, and EE to those measured by Douglas collections a total of n = 4 times per participant. Measurements were again completed twice with Fio2 of 0.4 as provided by the ventilator, and twice using the certified gas mixture as the source gas. No other changes were made to the patient’s ventilator settings. Time-averaged values for VO2, VCO2, and EE were calculated and compared to those measured simultaneously by Douglas technique using linear regression and Bland–Altman analysis. The CBS of the limits of agreement were calculated as previously described.

**Sample Size and Power Calculations**

Given that the in vivo experiments were planned at a set Fio2 (0.4), we based our sample size calculations on the mean bias (~3.1%) and its standard deviation (SD, 4.2%) of all experimental replicates at Fio2 of 0.4 in the in vitro experiment. Assuming that the system performed with the same accuracy in vivo (which we considered reasonable given the matching of experimental conditions to the expected clinical scenario), the inclusion of n = 12 patients allowed us to detect a 20% difference between device and reference measurements (which would be considered clinically acceptable) with 90% power and an α level of .05.

**RESULTS**

**Device Accuracy In Vitro**

There were no significant associations between tidal volume (range, 4–20 mL) or RR (range, 20–80 bpm) and percent difference between the MFC and device readings for either VO2 or VCO2 (Figure 2). There were also no significant Fio2-dependent differences in MFC-device percent difference in VCO2 readings. When compared to readings at Fio2 of 0.21, the percent difference (ie, error) between MFC settings and device VO2 measurements was significantly greater at an Fio2 of 0.8 than at Fio2 of 0.7 or less (P = .0003; Supplemental Digital Content 2, Figure 1, http://links.lww.com/AA/C279). Thus, we concluded that the upper limit of functionality of the device was Fio2 of 0.7; note that data for Fio2 of 0.8 were excluded from subsequent analysis.

VO2 measured by the device was similar to that of the MFC (Figure 3). The slope of the linear regression line was 1.002 (95% confidence interval [CI], 0.991–1.014) and correlation was excellent (R2 = 0.994). The bias was +0.04 mL/min (SD of differences, 1.10 mL/min) and the 95% limits of agreement (LOA) were −2.11 and +2.20 mL/min (95% CI of lower LOA was −2.40 to −1.83 mL/min and of the upper LOA was +1.92 to +2.49 mL/min). VO2 measurements by the device differed by >20% from that set by the MFC in 5 of 183 (2.7%) of experimental replicates.

Similarly, measurement of VCO2 by the device closely approximated that set by the MFC (slope of linear regression line, 1.007 [1.004–1.010]; R2 > 0.999). The bias was +0.26 mL/min (SD, 0.31 mL/min) with limits of agreement of −0.36 to 0.89 mL/min (95% CI of lower LOA was −0.43 to −0.27 mL/min and of the upper LOA was +0.29 to +0.95 mL/min). VCO2 measurements by the device did not differ by >20% from that set by the MFC in any of the 183 (0%) of experimental replicates.

**Device Accuracy and Precision in Rodents**

Rodents exhibited a VO2 of 1.10 ± 0.20 mL/min/100 g by Douglas method. Device-measured VO2 correlated well with that from the Douglas method (R2 = 0.826; Figure 4A). The bias in VO2 was −0.02 mL/min (SD, 0.55 mL/min) with limits of agreements of −1.28 and 0.89 mL/min (95% CI of lower LOA was −1.54 to −1.01 mL/min and of the upper LOA was +0.62 to +1.15 mL/min). The mean VCO2 by Douglas method was 0.89 ± 0.12 mL/min/100 g, and device measurements correlated well with Douglas measurements (R2 = 0.915; Figure 4B). The bias in VCO2 was 0.16 mL/min (SD, 0.25 mL/min) with limits of agreement
and 5.61 kcal/d (95% CI of lower LOA was −8.89 to −5.71 kcal/d and of the upper LOA was +4.02 to +7.20 kcal/d) ($R^2 = 0.853$; Figure 4D). Bias in VO$_2$ was not significantly different for experimental replicates in which Fio$_2$ was provided by the ventilator versus the certified gas mixture of 40% Fio$_2$ (bias, −0.31 vs −0.11 mL/min; $P = .2$).

Device Accuracy and Precision in Ventilated Neonates and Infants

A clinical description of the patients included in the clinical study is included in Table. The average VO$_2$ of the cohort was 9.0 ± 2.5 mL/kg/min by Douglas method. Device-measured VO$_2$ correlated well with that from the Douglas method ($R^2 = 0.89$; Figure 5A). The bias in VO$_2$ was +0.22 mL/kg/min (SD, 0.87 mL/kg/min) with limits of agreement of −1.49 and +1.93 mL/kg/min (95% CI, −1.89 to −1.09 mL/kg/min and +1.53 to +2.34 mL/kg/min). Mean bias in VO$_2$ was +2.56% ± 11.60% of the reading with 95% limits of agreement of −20.2% to 25.3%. Among 56 experimental replicates from 14 patients, only 6 VO$_2$ measurements fell outside of a 20% difference (Supplemental Digital Content 3, Figure 2A, B, http://links.lww.com/AA/C280), and no patient had >1 experimental replicate with a >20% difference.

The mean VCO$_2$ by Douglas method was 8.1 ± 2.3 mL/kg/min, and device measurements correlated well with Douglas measurements ($R^2 = 0.88$; Figure 5B). The bias in VCO$_2$ was 0.33 mL/kg/min (SD, 0.82 mL/kg/min) with limits of agreement of −1.27 and +1.94 mL/kg/min (95% CI, −1.65 to −0.89 mL/kg/min and +1.56 to +2.32 mL/kg/min). Mean bias in VCO$_2$ was +4.25% ± 11.20% of the reading with 95% limits of agreement of −17.7% to 26.2%. Like the error patterns in VO$_2$, only 6 VCO$_2$ measurements fell outside of the 20% difference (Supplemental Digital Content 3, Figure 2C, D, http://links.lww.com/AA/C280), and no patient had >1 experimental replicate with a >20% difference.

Device-measured RQ exhibited a bias of 0.015 (SD, 0.071) with limits of agreement of −0.12 and 0.15 (95% CI, −0.17 to −0.08 and +0.11 to +0.20), and correlation was modest ($R^2 = 0.568$; Figure 5C). The average EE was 63.9 ± 17.8 kcal/kg/d by Douglas, and the device exhibited a bias of +1.78 kcal/kg/d (SD, 5.96 kcal/kg/d) with limits of agreement of −9.89 and +13.50 kcal/kg/d (95% CI, −12.66 to −7.14 kcal/kg/d and +10.70 to +16.22 kcal/kg/d) ($R^2 = 0.89$; Figure 5D).

**DISCUSSION**

We have shown that a device that incorporates precise time alignment of flow and gas measurements within a mixed expired model exhibits what we would consider clinically acceptable bias and precision in VO$_2$, VCO$_2$, and EE, both in vitro and in vivo. The device performed equally well across a wide range of rates (up to 80 bpm) and also up to an Fio$_2$ of 0.7.

Currently available methods of measuring VO$_2$ include breath-by-breath, mixed expired, and Douglas bag methods. The AMIS 2000 (Innovision ApS, Odense, Denmark) is perhaps the most well-described instrument for use in the neonatal population.$^6,16–18$ This device incorporates a mass spectrometer for gas analysis but is unfortunately outdated, not available in the United States, and quite cumbersome to
Device for Oxygen Consumption in Neonates

Figure 3. In vitro accuracy of the device. Comparison of oxygen infused (ie, simulated VO$_2$) and carbon dioxide infused (ie, simulated VCO$_2$) by the mass flow controller and the VO$_2$ and VCO$_2$ measured by the device. Simulator and device VO$_2$ correlated well ($R^2 = 0.974$) with slope of the linear regression line being 1.023 (95% CI, 0.9964–1.049) (A), as it did for VCO$_2$ ($R^2 = 0.997$; slope of relationship, 1.026 [1.018–1.035]; B). Mean bias for VO$_2$ measurements was +0.04 mL/min (limits of agreement, −1.51 to 1.58 mL/min; C) and for VCO$_2$ was +0.25 mL/min (limits of agreement, −0.30 to 0.80 mL/min; D). In A–D, data are experimental replicates. In A–B, lines are linear regression line with 95% CI (dotted). In C–D, dotted lines are limits of agreement. Data include $F_{iO_2}$ up to 0.7. CI indicates confidence interval; VCO$_2$, carbon dioxide production; VO$_2$, oxygen consumption.

Figure 4. Correlation of device measurements with Douglas measurements in rodents. A, In rodents, device measurements of VO$_2$ correlated well with Douglas measurements ($R^2 = 0.826$; slope of linear regression line, 0.84 [0.73–0.95]; A), as did measurements of VCO$_2$ ($R^2 = 0.915$; slope of linear regression line, 0.89 [0.81–0.96]; B). Device estimates of RQ correlated modestly with Douglas measurements (C; $R^2 = 0.638$; slope of linear regression line, 0.78 [0.61–0.95]), as did EE estimates (D; $R^2 = 0.853$; slope of linear regression line, 0.86 [0.76–0.96]). EE indicates energy expenditure; RQ, respiratory quotient; VCO$_2$, carbon dioxide production; VO$_2$, oxygen consumption.
use. For these reasons, the device is no longer being produced or supported. Otherwise, the most well-studied device for monitoring VO₂ in the intensive care environment is the Deltatrac II Metabolic Monitor (Datex Ohmeda, Helsinki, Finland; and later Sensormedics, Yorba Linda, CA), which has long been considered a gold standard reference tool.₁⁹–₂⁷ This device has been shown to have a low mean bias but wide limits of agreement when compared with Douglas technique,²⁸ though the lower limit of validation testing has been VO₂ of 20 mL/min.²⁹ Although several studies have tested the Deltatrac in neonates and infants,²⁸–₃₁ the Deltatrac is also no longer being manufactured. Currently, several devices are available for the continuous monitoring of VO₂ and EE in ventilated patients, and our group has experience with 2 of them (Datex Ohmeda, GE Healthcare: E-COVX and E-CAiOVX module; GE Healthcare, Helsinki, Finland). Unfortunately, the neonatal range is outside the manufacturer’s recommended use for either of these modules. In our experience,⁸,⁹ they perform poorly in small infants, particularly in those breathing spontaneously (ie, RR above 40 bpm) or in those with low VO₂.

In assessing previous devices, several groups have considered a 20% limit of agreement to be clinically acceptable in the comparison of reference and device measurements.⁸,²₈

Table. Clinical Description of the Patients Included in the Clinical Validation Study

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Average RR (bpm)</th>
<th>% Leak</th>
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<tr>
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<td>2 mo</td>
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<tr>
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<td>2.9</td>
<td>35.3</td>
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<td>Complete atrioventricular canal</td>
<td>3 mo</td>
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<td>5</td>
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<td>42.7</td>
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<tr>
<td>5</td>
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<td>2 d</td>
<td>2.4</td>
<td>27.2</td>
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</table>

The mean RR during the sampling periods is recorded.
Abbreviations: d-TGA, d-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; NEC, necrotizing enterocolitis; RR, respiratory rate.

Figure 5. Correlation of device measurements with Douglas measurements in neonates and infants. A, In neonates and infants, device measurements of VO₂ correlated well with Douglas measurements (R² = 0.89; slope of linear regression line, 1.01 [0.95–1.06]; A), as did measurements of VCO₂ (R² = 0.88; slope of linear regression line, 0.98 [0.92–1.04]; B). Device estimates of RQ correlated modestly well with Douglas measurements (C; R² = 0.57; slope of linear regression line, 0.78 [0.63–0.92]), and EE correlated well (D; R² = 0.89; slope of linear regression line, 0.96 [0.88 to 1.05]). EE indicates energy expenditure; RQ, respiratory quotient; VCO₂, carbon dioxide production; VO₂, oxygen consumption.
However, these studies typically describe errors in devices that target VO₂ measurements in the 50–200 mL/min range, such that a 20% error represents a 10–40 mL/min measurement error. In our case, we found that 10.7% of experimental replicates exhibited >20% difference when the reference standard for VO₂ and VCO₂ was set by the MFC (rather than oxygen sensors). This is corroborated by the low incidence of error (2.7% of VO₂ measurements and 0% of VCO₂ measurements exhibited >20% difference) when the reference standard for VO₂ and VCO₂ was set by the MFC (rather than oxygen sensors). Note that the majority of confounding variables in that experiment were similar to the clinical experiment, including tidal volume, equipment, tubing, the presence of humidity, and rapid RR, such that a significant portion of the error may be related to the Douglas technique. Further, the poor correlation found in RQ measurements may have represented compounding error in the parameters from which it is derived, VO₂ and VCO₂. For example, although we were careful to flush the Douglas bag with inspired gas several times before each use, a small fraction of air contamination of the Douglas bag would lower fraction of expired oxygen (FEO₂) (which was ~39%), leading to an overestimate of VO₂ and simultaneously would lower fraction of expired carbon dioxide (FECO₂), leading to an underestimate of VCO₂, thus compounding an error in RQ estimate. The poor correlation in RQ may also be related to the mathematically narrow range of possible results for RQ. As noted by Bland and Altman, the strength of correlation depends on the range of possible values within the true quantity in the sample.³³

The accurate determination of VO₂ at elevated FiO₂, rapid RR, and low VO₂ requires accuracy in measurements in respiratory flow, O₂, and CO₂ measurements. Small errors in any of these composite measures lead to future confounding error in VO₂ or VCO₂. Several features of our device were specifically designed to optimize accuracy. First, it quantifies total inspiratory flow of dry gas and compensates for FiO₂-dependent changes in viscosity. FiO₂ is calculated using flow-weighted rather than time-weighted averaging, creating more accurate estimates of both volume, inspiratory flow, and FiO₂. The Haldane transformation is then used to also estimate expiratory volume flow. Second, the device uses single sensors to quantify partial pressures of O₂ and CO₂ on both the inspiratory and expiratory limbs, using a solenoid valve to alternate gas flow between the two. Considering the fluctuations in FiO₂, the timing algorithm uses circuit volumes and measured flow rates to determine the optimum cycle time between inspiratory and expiratory gas sampling by estimating the gas transport time between inspiratory and expiratory sampling points. This allows the quantification of O₂ and CO₂ concentrations on essentially the same sample of gas from the inspiratory and expiratory limbs. Third, several aspects of the device are optimized for long-term monitoring in the ICU. No expiratory or proximal flow sensor is applied and flow is determined on only dry gas, avoiding water condensation within the flow sensor (ie, rain-out). In our experience, this has been a significant impediment to existing technologies in the ICU environment. Further, the gas sampling rate is 60 mL/min, lower than any other device on the market, making interference with flow triggered ventilation less likely even in neonates. We did not note any ventilator alarms related to the device in the conduct of these animal experiments. Because the sites of gas sampling are remote from the Y piece, minimal dead space is added to the circuit and the risk of tracheal tube displacement is minimized. Further, our system minimizes errors related to gas analyzer response time and signal time alignment that limit the utility of current systems in rapidly breathing patients. Such systems use breath-by-breath sidestream analyzers in which gas is sampled from a single location most proximate to the patient (eg, just before the tracheal tube), where O₂ and CO₂ concentrations change rapidly as the sampled gas changes from inspired to expired gas with each breath. This makes response times and time alignment critical to accurately discern inspired and expired gas fractions. In our system, inspiratory and expiratory gases are separately sampled from the respective limbs of the circuit, where O₂ and CO₂ concentrations change orders of magnitude more slowly than they do at the single proximal sampling point. This makes response times and time alignment less critical, while also permitting a lower gas sampling rate.

**Limitations**

1. In the rodent validation experiment, we used the same O₂ and CO₂ sensors to measure gases in both the device as well as the Douglas method. Although these sensors are industry standard sensors and were calibrated before each use, the validation was limited to that of volume and flow. Errors in the O₂ or CO₂ measurements would have been missed.

2. In the rodent experiment, we were unable to reexamine the extremes of RR that we did in vitro, as they caused disturbances in acid-base balance and the steady-state condition.

3. The clinical validation study was not intended to detect differences in device accuracy based on patient variables. However, because we were satisfied with device performance, we did not feel the need to examine for such differences. Further, the reference (ie, Douglas) measurements were limited by the size of the bag (5 L), which limited gas collection in most infants (particularly those which were more tachypneic) to a 3- to 5-minute sampling period. The observed differences may have been even smaller had a larger bag been utilized.

4. Although we did not observe any intrabreath variation in mixed expired O₂ and CO₂ concentrations, it is possible that at larger tidal volumes, an expiratory mixing chamber might be required.

5. The device is currently unable to measure or compensate for air leak, which may lead to over- or underestimation of VO₂ and VCO₂. This device measures total gas flow at the inspiratory limb and would therefore be ignorant of downstream gas leak. The magnitude and direction of the error caused by a leak would depend on the composition of the leaked gas. In most cases, it is likely that the majority of leaked gas would be inspiratory (eg, during peak inspiratory pressure). This would result in an overestimate in total inspiratory gas volume without a change in FEO₂.
resulting in an overestimate of VO$_2$. However, the impact will be limited to typically 1/3 of the “tidal volume leak percentage” because the total flow measured in the inspiratory limb (used in Equations 1 and 2) includes the bias flow and the compliance effect in addition to the minute ventilation. Conversely, if CO$_2$ is present in the leaking gas (ie, expiratory contamination), the error would be smaller, and if the leaking gas and mixed expired gas concentrations are equal, the error will be negligible. If the leaked air represented alveolar gas (eg, tracheal leak), VO$_2$ may be underestimated. In our first iteration, leak detection took place by comparison of inspiratory and expiratory tidal volumes on the ventilator. Ideally, this device would be incorporated into a ventilator, permitting for the incorporation of both inspiratory and expiratory flow measurements, enabling a leak compensation algorithm.

**CONCLUSIONS**

A device that incorporates precise timing of inspiratory and expiratory gas measurements within a mixed expired model quantifies VO$_2$, VCO$_2$, and EE with clinically acceptable bias and precision in the neonatal range, including up to RRs of 80 bpm and FiO$_2$ as high as 0.7.

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**DISCLOSURES**

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Device for Oxygen Consumption in Neonates