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 (VO_2) 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 VO_2, 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 VO_2 and carbon dioxide production (VCO_2) 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, VO_2, VCO_2, 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 VO_2 was +0.04 ± 1.10 (95% limits of agreement, −2.11 to +2.20) mL/min and VCO_2 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 VO_2, +0.16 ± 0.25 (−0.32 to +0.65) mL/min for VCO_2, and −0.84 ± 3.29 (−7.30 to +5.61) kcal/d for EE. In infants, the mean VO_2 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 VCO_2 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 VO_2 and +4.25% ± 11.20% of the reading for VCO_2; 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 VO_2 or VCO_2.

CONCLUSIONS: This device can measure VO_2, VCO_2, 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.

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Boston Children's Hospital (B. D. Polizzotti and J. N. Kheir) and InnoCC (P. Clemensen.) are in the process of filing a patent entitled "Oxygen Consumption and Energy Expenditure Monitoring in Infants and Children" describing the methods described herein.

Clinical trial registry number: NCT03154112; https://clinicaltrials.gov/ct2/show/NCT03154112.

Reprints will not be available from the authors.

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The accurate measurement of energy expenditure (EE) and oxygen consumption (VO_2) 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.[1] The underestimation of EE may lead to underfeeding and inadequate caloric provision, and may worsen clinical outcomes.[2] Alternatively, overestimation of EE may lead to overfeeding, may increase carbon dioxide (CO_2) production (VCO_2), and prolong the duration of mechanical ventilation.[2] Overestimation of EE, whether by inaccurate measurement or by the use of estimating equations,[3] 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%.[4] Fluctuations in metabolic rate, temperature, activity level, and overall health are clearly determinants of EE that are not captured in equations.[3] Thus, the accurate quantification of EE in ventilated neonates is highly desirable.

Like EE, VO_2 varies greatly between health and illness and may permit identification of critical illness states. An increased VO_2 (or VCO_2) may be the first signs of fever, systemic inflammatory response, seizure, or agitation in ventilated patients, permitting early clinical intervention. Alternatively, VO_2 may decrease in patients with severe low cardiac output syndrome.[5] Further, VO_2 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 VO_2.[6] As with EE, small discrepancies in equation-based estimates of VO_2 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 VO_2 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.[7–9] To address this important problem, we have created a new device focused on the quantification of EE and VO_2 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, VO_2 and VCO_2 are measured through the accurate quantification of inspired and expired oxygen (O_2) and CO_2 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 H_2O 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 O_2 laser diode sensor (Oxigraf, CA) and infrared CO_2 sensor (Oxigraf, Sunnyvale, CA). Expired gas is collected at the ventilator exhaust and is similarly analyzed. A single set of O_2 and CO_2 sensors is used for the measurements of inspiratory and expiratory gas 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 O_2 and CO_2 concentrations on essentially the same sample of gas from the inspiratory and expiratory limbs in sequence.

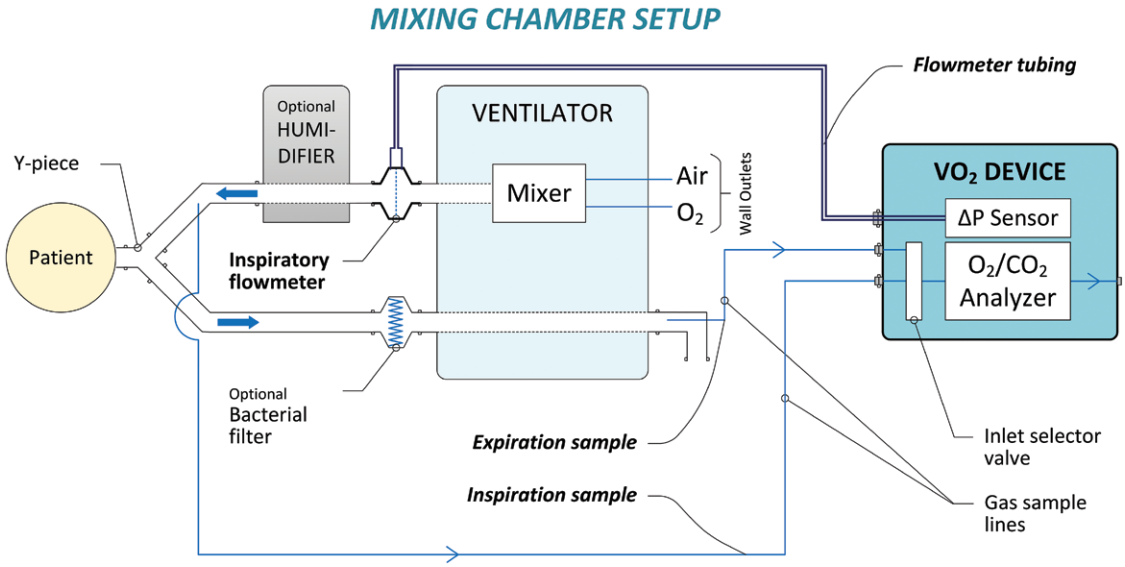

Figure 1. Schematic of device attachments. The device quantifies inspiratory flow using a flowmeter at the inspiratory port from the ventilator, before the humidifier. Inspired gas is sampled distal to the humidifier to permit maximal mixing. Expiratory gas is sampled at the ventilator exhaust, also to maximize mixing. O_2 and CO_2 are each analyzed by single analyzers within the device, which alternately analyzes inspiratory and expiratory gases using a solenoid valve. CO_2 indicates carbon dioxide; O_2, oxygen; VO_2, oxygen consumption; ΔP, differential pressure.

VO_2 (mL/min at standard temperature and pressure dry) is calculated according to Equation 1, where F_I is the fractional inspired and F_E is the fractional mixed expired concentrations of O_2 and CO_2:

$$VO_2(\text{STPD}) = V'_{I,tot}(\text{ATPD}) \times \frac{273}{273+t_{amb}} \times \frac{P_B}{760} \times \frac{F_IO_2 \times (1-F_ECO_2) - F_EO_2 \times (1-F_ICO_2)}{1-F_EO_2-F_ECO_2} \quad (1)$$

VCO_2 is calculated according to Equation 2 as follows:

$$VCO_2(\text{STPD}) = V'_{I,tot}(\text{ATPD}) \times \frac{273}{273+t_{amb}} \times \frac{P_B}{760} \times \frac{F_ECO_2 \times (1-F_IO_2) - F_ICO_2 \times (1-F_EO_2)}{1-F_EO_2-F_ECO_2} \quad (2)$$

Total inspiratory gas flow $V'_{I,tot}$ (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 (F_IO_2), 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 volume flows from the equations, making only inspiratory volume flows necessary. The barometric pressure (P_B [mm Hg]) is not adjusted for water vapor pressure because the gas is dry. Ambient temperature (t_{amb} [°C]) is measured by the device. F_I and F_E are fractional concentrations of dry gas because Nafion tubing was used to equilibrate the humidity of sampled gas with that of ambient air, both during measurements and during calibrations using dry gas mixtures. Measured fraction of inspired carbon dioxide (F_ICO_2) was measured (0.0000–0.0001) but could alternatively be left out. Because intrabreath F_IO_2 may vary considerably around the set F_IO_2 even on the most advanced ventilators, we calculated flow-weighted averages of measured F_IO_2 for use in the equations, that is, the product of instantaneous flow and time-shifted O_2 concentration was integrated and divided by integrated flow. F_E is determined by simple averaging during expirations.

EE (kcal/d) is calculated according to Equation 3, the modified Weir equation without correction for protein metabolism[10]:

$$EE = (3.941 \times VO_2 + 1.106 \times VCO_2) \times 1440 \quad (3)$$

Because we use the same sensors to quantify O_2 and CO_2 (respectively) in inspired and expired gas, the variables 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 (VO_2, VCO_2, and EE) is generated at this interval.

The flowmeter was linearized[11] before each study, and calibrated daily for unidirectional measurement using a 1-L calibration syringe (Hans Rudolph, Shawnee, KS). O_2 and CO_2 sensors were calibrated using room air, O_2 (Airgas, Boston, MA), and 5% CO_2/20% O_2/balance N_2, 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% CO_2 and 50% O_2, ±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 VCO_2 and half of the rate would simulate a negative VO_2 (O_2 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). F_IO_2 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 VO_2 and VCO_2 were varied between 4 and 20 mL/min through manipulation of the MFC. The resulting mixed expired CO_2 concentrations were in the range 0.5%–1.6%. Matrix design was intended to interrogate the lower limit of detection in VO_2 at the highest RR and F_IO_2. Measured VO_2 and VCO_2 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 F_IO_2 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 VO_2 or VCO_2 and the MFC setting was compared against F_IO_2 or RR.[12]

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 H_2O, peak inspiratory pressure 20 cm H_2O, and F_{IO_2} 0.4. RR was varied at either 30 or 50 bpm.

VO_2, VCO_2, and EE were measured by the device, a total of n = 4 times per animal. In 2 replicates, the F_{IO_2} was provided by the ventilator as in clinical practice and the volume-averaged inspired O_2 content was measured by the device. In the other 2 replicates, a certified gas mixture (40% ± 0.03% F_{IO_2} absolute accuracy; Airgas, Boston, MA) was used as the source gas. This provided a gold standard measure of inspired O_2 content for use in Douglas calculations (to determine whether the experimental mathematical coupling that takes place when the device is used to calculate inspired O_2 content for Douglas collections exhibits significantly different results). In all replicates, expired O_2 and CO_2 content were quantified using a Douglas technique. Briefly, a 5-L nondiffusing 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 O_2 and CO_2 using the device's internal sensors for calculation of a reference standard VO_2, VCO_2, and EE. Time-averaged values for VO_2, VCO_2, 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 VO_2 and VCO_2 was different between replicates in which the F_{IO_2} was set using the ventilator versus certified tank using an unpaired *t* test. Note that we analyzed differences as both absolute values and as percentages of total, as we felt both to be clinically important (ie, knowing that error in VO_2 is ±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 VO_2, VCO_2, and EE to those measured by Douglas collections a total of n = 4 times per participant. Measurements were again completed twice with F_{IO_2} 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 VO_2, VCO_2, and EE were calculated and compared to those measured simultaneously by Douglas technique using linear regression and Bland–Altman analysis. The CIs of the limits of agreement[13] were calculated as previously described.[14]

Sample Size and Power Calculations

Given that the in vivo experiments were planned at a set F_{IO_2} (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 F_{IO_2} 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[15]) 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 VO_2 or VCO_2 (Figure 2). There were also no significant F_{IO_2}-dependent differences in MFC-device percent difference in VCO_2 readings. When compared to readings at F_{IO_2} of 0.21, the percent difference (ie, error) between MFC settings and device VO_2 measurements was significantly greater at an F_{IO_2} of 0.8 than at F_{IO_2} 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 F_{IO_2} of 0.7; note that data for F_{IO_2} of 0.8 were excluded from subsequent analysis.

VO_2 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 (R^2 = 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). VO_2 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 VCO_2 by the device closely approximated that set by the MFC (slope of linear regression line, 1.007 [1.004–1.010]; R^2 > 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 +0.79 to +0.95 mL/min). VCO_2 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 VO_2 of 1.10 ± 0.20 mL/min/100 g by Douglas method. Device-measured VO_2 correlated well with that from the Douglas method (R^2 = 0.826; Figure 4A). The bias in VO_2 was −0.20 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 VCO_2 by Douglas method was 0.89 ± 0.12 mL/min/100 g, and device measurements correlated well with Douglas measurements (R^2 = 0.915; Figure 4B). The bias in VCO_2 was 0.16 mL/min (SD, 0.25 mL/min) with limits of agreement

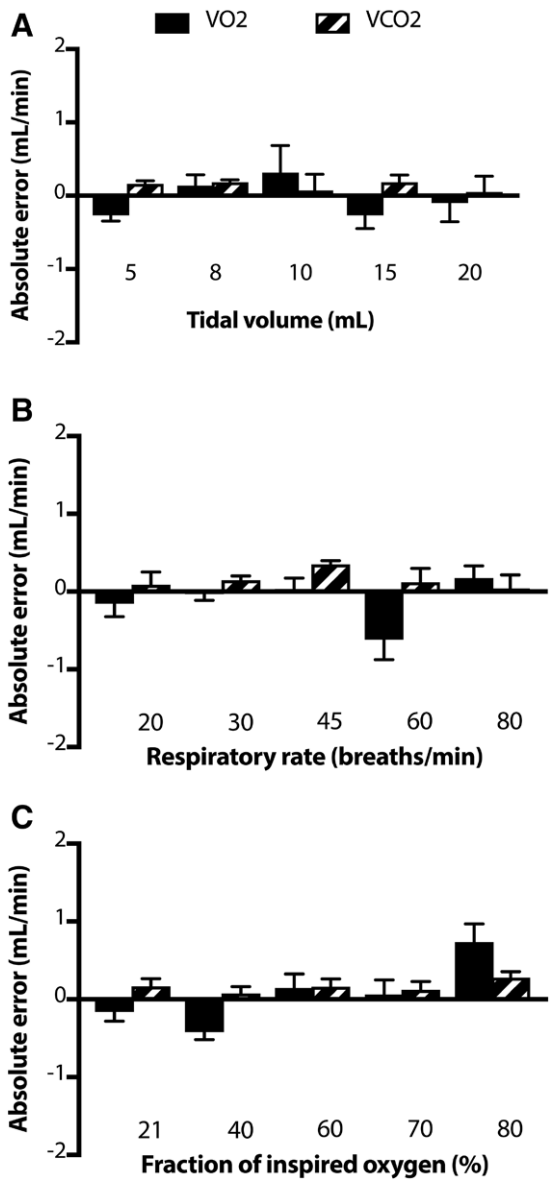

Figure 2. Error (ie, difference between device and MFC) estimates in VO_2 and VCO_2 measurements. In benchtop simulation experiments, there was no change in the absolute error of either VO_2 (solid black; $P = .95$) or VCO_2 (striped black; $P = .95$) as a function of tidal volume (A) or respiratory rate (B; $P = .91$ for VO_2 and $P = .78$ for VCO_2). C, When assessed as a function of FIO_2, error in VO_2 measurements did not vary with FIO_2 at or below 0.7 ($P = .09$), but did at FIO_2 of 0.8 ($P = .0003$). Error in VCO_2 did not vary with FIO_2 ($P = .94$). Data are means, error is SEM. Number of experimental replicates in each group is as shown in Table. All analyses performed by 1-way ANOVA with Dunn correction for multiple comparisons. ANOVA indicates analysis of variance; FIO_2, fraction of inspired oxygen; MFC, mass flow controller; SEM, standard error of the mean; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

of −0.32 and 0.65 mL/min (95% CI of lower LOA was −0.44 to −0.20 mL/min and of the upper LOA was +0.53 to +0.77 mL/min). Device-measured RQ exhibited a bias of 0.04 (SD, 0.06) with limits of agreement of −0.07 and 0.15 (95% CI, −0.11 to −0.03 and +0.11 to +0.20) though correlation was modest ($R^2 = 0.638$; Figure 4C). EE exhibited a bias of −0.84 kcal/d (SD, 3.29 kcal/d) with limits of agreement of −7.30 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

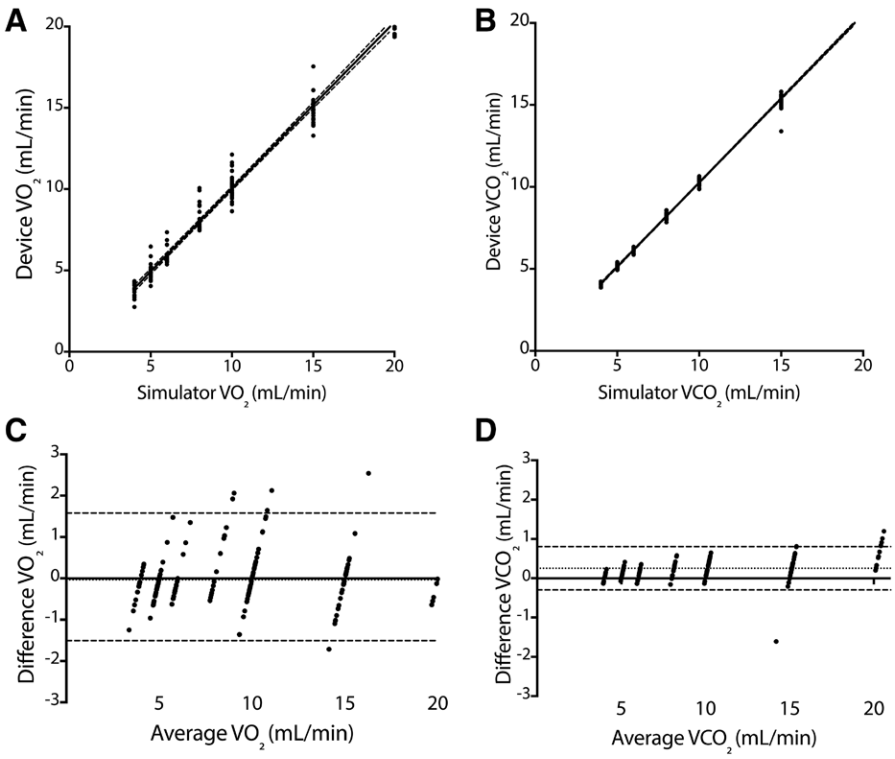

Figure 3. In vitro accuracy of the device. Comparison of oxygen infused (ie, simulated VO_2) and carbon dioxide infused (ie, simulated VCO_2) by the mass flow controller and the VO_2 and VCO_2 measured by the device. Simulator and device VO_2 correlated well (R^2 = 0.974) with slope of the linear regression 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.

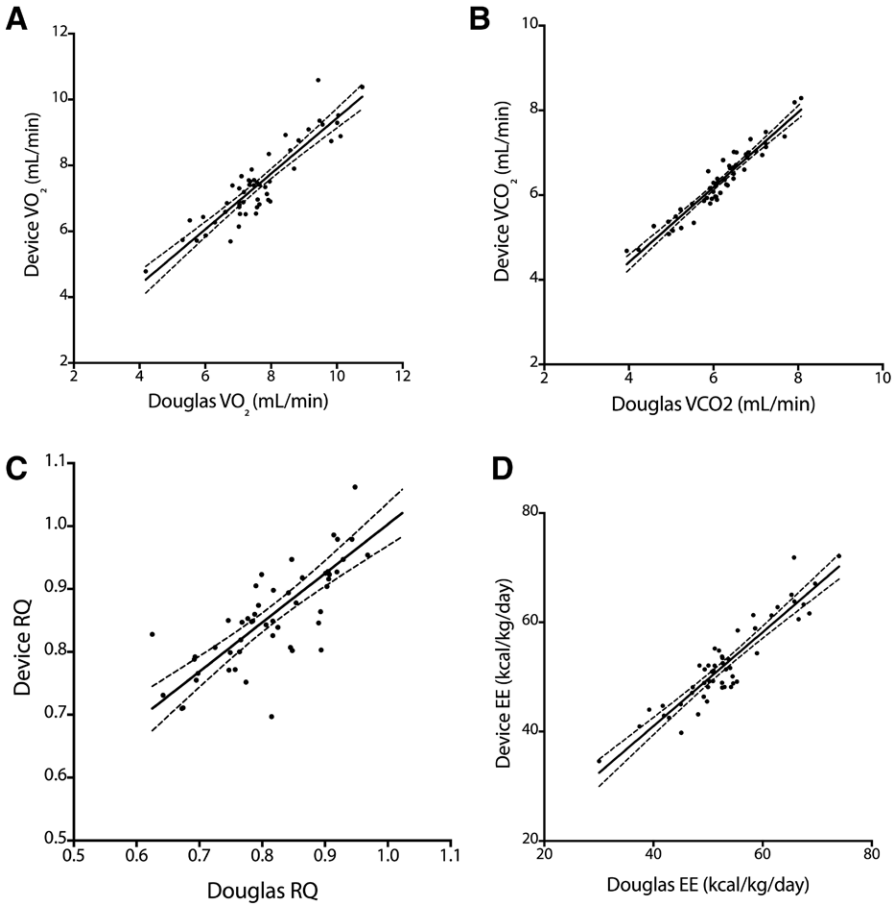

Figure 4. Correlation of device measurements with Douglas measurements in rodents. A, In rodents, device measurements of VO_2 correlated well with Douglas measurements (R^2 = 0.826; slope of linear regression line, 0.84 [0.73–0.95]; A), as did measurements of VCO_2 (R^2 = 0.915; slope of linear regression 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.

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

No.	Diagnosis	Age	Weight (kg)	Average RR (bpm)	% Leak
1	Omphalocele	2 mo	5.2	33.7	10
2	Sepsis	4 mo	2.9	35.5	30
3	Complete atrioventricular canal	3 mo	3.2	36.6	5
4	Critical pulmonary stenosis	4 d	2.7	42.7	<15
5	Critical pulmonary stenosis	2 d	2.4	27.2	7
6	Aortic coarctation, ventricular septal defect	4 d	3.7	32.0	5
7	HLHS	3 d	3.5	14.4	5
8	HLHS	7 d	3.1	22.0	<5
9	Omphalocele	3 mo	5.1	60.6	8
10	Bronchomalacia	4 mo	2.7	38.9	10
11	d-TGA	5 d	2.5	47.5	7
12	d-TGA	12 d	4.0	28.0	25–30
13	HLHS	18 d	3.0	30.0	5–10
14	NEC, prematurity	16 d	0.83	49.3	0

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.

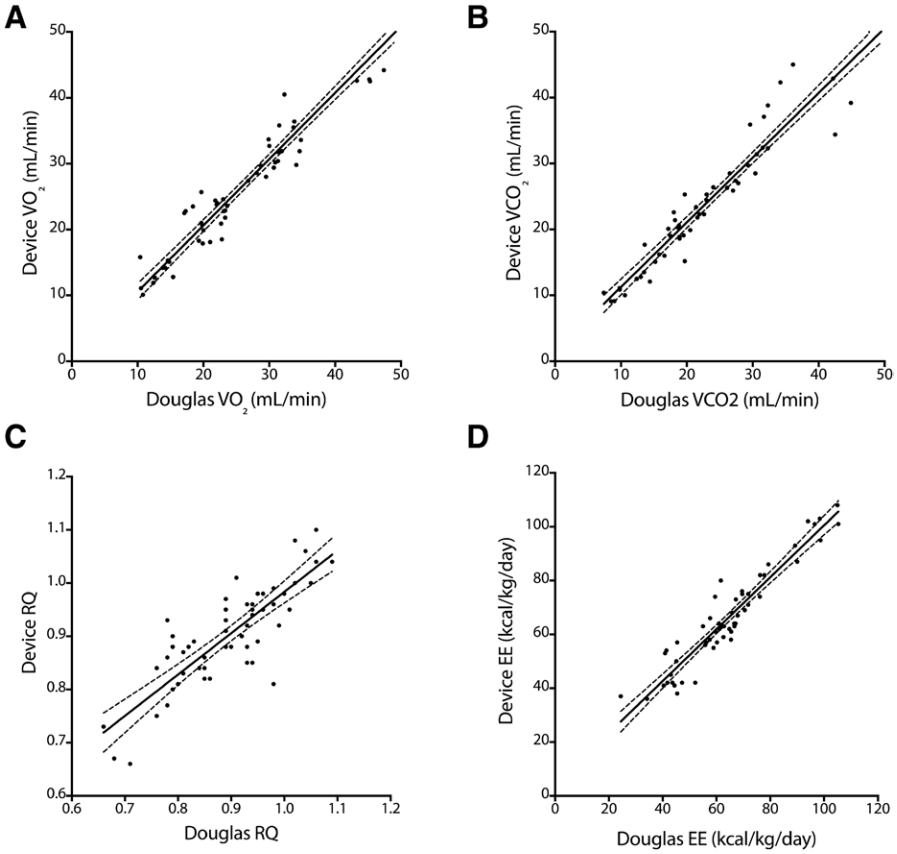

Figure 5. Correlation of device measurements with Douglas measurements in neonates and infants. A, In neonates and infants, device measurements of VO_2 correlated well with Douglas measurements (R^2 = 0.89; slope of linear regression line, 1.01 [0.95–1.06]; A), as did measurements of VCO_2 (R^2 = 0.88; slope of linear regression line, 0.98 [0.92–1.04]; B). Device estimates of RQ correlated modestly well with Douglas measurements (C; R^2 = 0.57; slope of linear regression line, 0.78 [0.63–0.92]), and EE correlated well (D; R^2 = 0.89; slope of linear regression line, 0.96 [0.88 to 1.05]). 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 VO_2 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 VO_2 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 VO_2 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 VO_2.

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]

However, these studies typically describe errors in devices that target VO_2 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 measurements fell outside of this range, though in no patient was >1 of the 4 measurement replicates outside of the 20% error range, such that if values are measured continuously at the bedside (and therefore averaged over time), this error should become averaged out. Further, it is possible that these errors were in part due to error in the Douglas technique, which is thought to itself carry a 15% error rate.[25,32] This is corroborated by the low incidence of error (2.7% of VO_2 measurements and 0% of VCO_2 measurements exhibited >20% difference) when the reference standard for VO_2 and VCO_2 was set by the MFC (rather than Douglas). 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, VO_2 and VCO_2. 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 (F_EO_2) (which was ~39%), leading to an overestimate of VO_2 and simultaneously would lower fraction of expired carbon dioxide (F_ECO_2), leading to an underestimate of VCO_2, 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 VO_2 at elevated FIO_2, rapid RRs, and low VO_2 requires accuracy in measurements in respiratory flow, O_2, and CO_2 measurements. Small errors in any of these composite measures lead to future compounding error in VO_2 or VCO_2. Several features of our device were specifically designed to optimize accuracy. First, it quantifies total inspiratory flow of dry gas and compensates for FIO_2-dependent changes in viscosity. FIO_2 is calculated using flow-weighted rather than time-weighted averaging, creating more accurate estimates of both volume, inspiratory flow, and FIO_2. The Haldane transformation is then used to also estimate expiratory volume flow. Second, the device uses single sensors to quantify partial pressures of O_2 and CO_2 on both the inspiratory and expiratory limbs, using a solenoid valve to alternate gas flow between the two. Considering the fluctuations in FIO_2, 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 O_2 and CO_2 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 O_2 and CO_2 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 O_2 and CO_2 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 O_2 and CO_2 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 O_2 or CO_2 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 O_2 and CO_2 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 VO_2 and VCO_2. 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 F_EO_2,

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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Conflicts of Interest: None.
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