Bymixer system can measure O₂ uptake and CO₂ elimination in the anesthesia circle circuit

[Un système mélangeur (bymixer) peut mesurer le captage d'O₂ et l'élimination du CO₂ dans le circuit anesthésique en cercle]

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Background: The ability to measure carbon dioxide elimination ($\dot{V}_{CO_2}$), oxygen uptake ($\dot{V}_{O_2}$), and R (respiratory exchange ratio, $\dot{V}_{CO_2}/\dot{V}_{O_2}$) during anesthesia may help the non-invasive detection of critical events (e.g., abrupt decrease in cardiac output) and metabolic upset (e.g., onset of anaerobic metabolism).

Methods: We have developed a new clinical bymixer (inline mixing chamber) that can measure mixed inspired and expired gas fractions in the anesthesia circle circuit. The addition of a standard anesthesia gas analyzer and flowmeter, and a new airway temperature and humidity sensor, allow determinations of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ at the airway opening of the circle circuit. Over a range of tidal volume and frequency, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were compared to reference values generated by the combustion of metered liquid ethanol in a new metabolic lung simulator.

Results: By linear regression, bymixer-flow measurements of $\dot{V}_{CO_2}$ (slope = 1.02, Y-intercept = -5.31, coefficient of determination, $R^2 = 0.998$) and $\dot{V}_{O_2}$ (slope = 1.05, Y-intercept = -4.34, $R^2 = 0.993$) correlated closely to the reference values generated by the metabolic lung simulator. Limits of agreement analysis generated percent errors (mean $\pm$ 1.96 SD) of $-1.2 \pm 7.2\%$ for $\dot{V}_{CO_2}$ and $2.5 \pm 9.8\%$ for $\dot{V}_{O_2}$.

Conclusions: The new clinical bymixer is compact, lightweight, disposable, inexpensive, and has a fast and adjustable response time (time constant about 14 sec). Anesthesia circle circuit integrity is maintained. Bymixer-flow measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ are accurate and may add to clinical monitoring under anesthesia and surgery.

Contexte : La faculté de mesurer l'élimination du dioxyde de carbone ($\dot{V}_{CO_2}$), le captage d'oxygène ($\dot{V}_{O_2}$) et R (taux d'échange respiratoire, $\dot{V}_{CO_2}/\dot{V}_{O_2}$) pendant l'anesthésie pourrait favoriser une détection non-invasive d'événements critiques (par ex., une diminution abrupte du débit cardiaque) et d'un bouleversement métabolique (par ex., déclenchement d'un métabolisme anaérobie).

Méthode : Nous avons développé un nouveau mélangeur clinique (chambre de mélange en ligne) pouvant mesurer les fractions des gaz inspirés et expirés mélangés dans le circuit anesthésique en cercle. L'ajout d'un analyseur de gaz anesthésique standard et d'un débitmètre, ainsi que d'un nouveau capteur de température et d'humidité des voies aériennes, permet de déterminer les valeurs de $\dot{V}_{CO_2}$ et de $\dot{V}_{O_2}$ au site d'ouverture des voies aériennes du circuit en cercle. Les $\dot{V}_{CO_2}$ et $\dot{V}_{O_2}$ ont été comparées à des valeurs de référence générées par la combustion d'éthanol liquide calibré dans un nouveau simulateur pulmonaire métabolique, en faisant varier le volume courant et la fréquence.

Résultats : Selon une analyse de régression linéaire, le mélangeur donnait des mesures de $\dot{V}_{CO_2}$ (pente = 1,02, ordonnée à l'origine = -5,31, coefficient de détermination, $R^2 = 0,998$) et de $\dot{V}_{O_2}$ (pente = 1,05, ordonnée à l'origine = -4,34, $R^2 = 0,993$) en étroite corrélation avec les valeurs de référence générées par le simulateur pulmonaire métabolique. Les limites d'analyse de concordance ont généré des pourcentages d'erreurs de (moyenne $\pm$ 1,96 SD) de $-1,2 \pm 7,2\%$ pour $\dot{V}_{CO_2}$ et de $2,5 \pm 9,8\%$ pour $\dot{V}_{O_2}$.

Conclusion : Le nouveau mélangeur clinique est compact, léger, jetable, bon marché, et a un temps de réaction rapide et ajustable (constante de temps environ 14 sec). L'intégrité du circuit anesthésique en cercle est maintenue. Les mesures de débit du mélangeur pour $\dot{V}_{CO_2}$ et $\dot{V}_{O_2}$ sont précises et pourraient ajouter au monitoring clinique pendant l'anesthésie et la chirurgie.

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Competing interests: The fast response temperature and humidity airway sensor (U.S. patent # 6,014,890) and the bymixer (patent pending) are available for commercialization. The authors have no current competing interests with these technologies.

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INDIRECT calorimetry is a noninvasive technology for the measurement of metabolic gas exchange at the airway opening. Until now, it has been mainly used during intensive care medicine.¹⁻⁴ The ability to measure airway oxygen uptake ($\dot{V}O_2$) and carbon dioxide elimination ($\dot{V}CO_2$) during anesthesia by indirect calorimetry may help the detection and management of critical events during anesthesia, such as an abrupt decrease in cardiac output or onset of pulmonary embolism.⁵⁻¹⁰ Moreover, the respiratory exchange ratio ($R = \dot{V}CO_2/\dot{V}O_2$) is an index of cellular metabolism. An increase in R may signal onset of anaerobic metabolism.^{6,11}

Indirect calorimetry requires measurements of airway flow, inspired gas fractions, and mixed expired gas fractions. However, measurement of mixed expired gas fractions during anesthesia is problematic. In the common anesthesia circle circuit¹² (Figure 1), the classic method of gas collection from the expiratory outlet port is not valid, because much of the expired gas becomes part of the next inspiration. Furthermore, $\overline{F}ECO_2$ cannot be measured since CO_2 is completely removed by the absorber. Accordingly, we developed a new clinical bymixer⁵ (Figure 2) that is interposed in the expiratory limb of the anesthesia circle circuit. The bymixer allows the measurement of mixed gas fractions by diverting a constant portion of total flow through a mixing arm. The clinical bymixer is compact, disposable, remains free of condensed moisture or secretions, and has an adjustable and fast response.

We have previously validated the performance and accuracy of the clinical bymixer to allow measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ in a conventional open circuit ventilator.¹⁰ However, the anesthesia circle circuit poses a number of potential pitfalls. First, in-line mixing chambers are required to maintain the integrity of the anesthesia circle. Second, depending on the circle circuit design, during the end of expiration, inspired limb gas could flow across the Y-adapter and contaminate the expired limb gas concentrations. Third, the inspired O_2 fraction waveform is affected by both fresh gas flow settings and addition of gas from the previous expiration. The inspired O_2 fraction may vary with time during inspiration,^{1,13} especially during non-steady state conditions. Fourth, the presence of the CO_2 absorber requires a bymixer on the expired limb (and not on the ventilator exhaust gas port). Fifth, if carbon dioxide absorption is incomplete, inspired CO_2 may be present and must be measured. Sixth, moisture accumulation in the circle circuit could conceivably impact bymixer performance.

Accordingly, in this study we tested the ability of the clinical bymixer⁵ to measure $\dot{V}O_2$ and $\dot{V}CO_2$ in the

FIGURE 1 Validation of the bymixer-airway flow measurement in the new metabolic lung simulator. Gas was circulated, by precision roller pump ($5\text{ L}\cdot\text{min}^{-1}$), between the mechanical lung and the airtight metabolic chamber. In the metabolic chamber, stoichiometric reference values of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were generated by combustion of metered liquid ethanol, delivered by a precision syringe pump. The baffle prevented the flame from being extinguished by gas flow into the metabolic chamber. Water circulated through the surrounding bath to maintain constant temperature. A semi-closed anesthesia circle circuit/anesthesia machine ventilated the mechanical lung. New clinical bymixers (inline mixing chambers) were placed on both the inspiratory and expiratory limbs. A pneumotachometer cuvette and the fast response humidity and temperature sensor were positioned at the airway opening. Airway flow was converted to STPD conditions using the measured airway humidity and temperature. The bymixer-airway flow measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ were determined by applying the expired flow, inspired bymixer gas fractions, and mixed expired bymixer gas fractions to standard equations (equations 2 and 3, respectively). STPD = standard temperature and pressure dry; T = temperature; FGF = fresh gas flow; APL = adjustable pressure limiting.

anesthesia circle circuit. In addition to the expired limb bymixer, an inspired limb bymixer was utilized to flow-average any temporal variability of FIO_2 and measure any inspired CO_2 . Gas fractions and airway opening flow (pneumotachometry) were measured with a standard clinical monitor. A new fast-response airway sensor of humidity and temperature^A allowed conversion of indirect calorimetry values to standard temperature and pressure dry (STPD) conditions. (In our previous study of bymixer-flow measurements,¹⁰ the absence of STPD correction resulted in $\dot{V}CO_2$ and $\dot{V}O_2$ errors of 6.1% and 6.8%, respectively). The present study could not be performed in patients because there is no available accurate reference standard measurement of $\dot{V}CO_2$ and $\dot{V}O_2$ during anesthesia, steady

FIGURE 2 The new clinical bymixer (inline mixing chamber) splits total gas flow into main flow and bypass flow (mixing chamber). The mixing arm is constructed of corrugated tubing and a downstream sampling port and flow resistor. Flow-averaged mixed gas fractions are measured at the sampling port. Comparison of the bymixer flow-averaged measurements of PCO_2 to values measured in an exhaust gas collection (Douglas bag) demonstrated excellent correlation and agreement.⁵ Reprinted with permission from *Anesth Analg* 2003; 97: 1414–20.

state conditions are difficult to maintain and confirm in patients, and a wide range of $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$ cannot be generated during patient studies.¹⁰ Accordingly, we utilized a bench metabolic lung simulator (liquid ethanol combustion)¹⁴ to generate a wide range of accurate, adjustable, and stable reference values of $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$.

Methods

Indirect calorimetry calculations

$\dot{V}\text{O}_2$ is given by:

$$\dot{V}\text{O}_2 = \dot{V}\text{I} \cdot \text{FIO}_2 - \dot{V}\text{E} \cdot \text{FEO}_2 \quad \text{Equation 1}$$

where $\dot{V}\text{I}$ and $\dot{V}\text{E}$ are the inspired and expired minute volumes and FIO_2 and FEO_2 are the inspired and mixed expired O_2 fractions.^{5,10,15} For $\dot{V}\text{O}_2$, measurement of both inspired and expired $\dot{V}$ leads to substantial error (equation 1) because $\dot{V}\text{O}_2$ is a small number calculated as the difference of two large values (inspired $\dot{V}\text{O}_2$ and expired $\dot{V}\text{O}_2$).¹⁵ To accurately measure this difference, most airway flowmeters lack sufficient precision and zero stability and the extra volume in expired gas, due to increased warmth and added humidity compared to inspired gas, must be measured.¹⁶ To address these problems, the Haldane transformation is utilized, which invokes the conservation of the inert gas nitrogen during steady state ($\dot{V}\text{I} \cdot \text{FIN}_2 = \dot{V}\text{E} \cdot \text{FEN}_2$). By solving for $\dot{V}\text{I}$ and substitution into equation 1,

$$\dot{V}\text{O}_2 = \dot{V}\text{E} (\text{FIO}_2 \cdot \text{FEN}_2 / \text{FIN}_2 - \text{FEO}_2). \quad \text{Equation 2}$$

$\dot{V}\text{CO}_2$ is given by:

$$\dot{V}\text{CO}_2 = \dot{V}\text{E} \cdot \text{FECO}_2 - \dot{V}\text{I} \cdot \text{FICO}_2 \quad \text{Equation 3}$$

The Haldane transformation was also applied to the determination of $\dot{V}\text{CO}_2$. While CO_2 is generally absent from inspiration, accurate measurement of $\dot{V}\text{CO}_2$ must address the presence of CO_2 in inspired gas relative to the side-stream sampling site.⁸ In brief, the volume of gas in the common airway, between the connection of the inspired limb at the Y piece and the side-stream sampling site, contains CO_2 from the previous exhalation which becomes inspired CO_2 in the subsequent inhalation. The second term of the right side of equation 3 removes this small volume of inspired CO_2 to maximize accuracy of measured $\dot{V}\text{CO}_2$. This becomes especially important in scenarios of overt CO_2 rebreathing, such as exhausted CO_2 absorbant or malfunctioning circle circuit valves.¹⁷

NEW CLINICAL BYMIXER (PATENT PENDING)

To measure mixed gas fractions,¹⁸ we developed a mechanical clinical bymixer⁵ (Figure 2), which bypassed a constant portion of the main flow through the mixing chamber. The bypass channel was composed of a length of expandable/collapsible pediatric anesthesia circuit tubing, connected in series to a sampling port adapter and a flow resistor. In this study, the mixing arm length was set to 121 cm, which generated a mixing chamber volume (measured up to the sampling port) of 200 mL (time constant of about 14 sec). The main flow and bypass flow channels were connected at

each end by identical standard circle anesthesia circuit Y-adapters.

NEW METABOLIC LUNG SIMULATOR (FIGURE 1)^{14,19} The mechanical lung (Dual Adult TTL, Model 1600, Michigan instruments, Inc., Grand Rapids, MI, USA) was connected by a circular circuit to an airtight, rigid combustion chamber (5.7 L pressure cooker). The combustion chamber was glued to the bottom of a large, flat, open container. Tap water constantly flowed through a port into this container and flowed out of a second port into a sink drain, forming a constant temperature water jacket around the combustion chamber. An occlusive roller pump (15 mm internal diameter tubing; Precision Blood Pump, COBE Perfusion system, Lakewood, CO, USA) generated constant gas flow (5 L·min⁻¹) between the metabolic chamber and the lung simulator.

The inspired and expired limbs of the anesthesia machine (Narkomed 2A, North American Dräger, Telford, PA, USA) circle circuit joined at the Y-adapter. Clinical bymixers were interposed in the inspired and expired limbs of the circuit. In order, the Y-adapter was connected to the pneumotachometer cuvette (D-lite adapter, Capnomac Ultima, Datex Medical Instruments, Instrumentarium Corp., Helsinki, Finland), the humidity and temperature sensor (see below), and the mechanical lung. The mechanical lung was ventilated with 60% O₂ in nitrogen [fresh gas flow (FGF): 1 L·min⁻¹ O₂ and 1 L·min⁻¹ air]. At each level of alcohol combustion rate (and, hence, resultant CO₂ production and O₂ consumption), tidal volume (350–800 mL), respiratory frequency (7–12 min⁻¹) and inspiratory flow were adjusted to maintain end-tidal partial pressure of CO₂ (PETCO₂) near 40 mmHg. Before each study, the system was pressurized to 40 mmHg to check for leaks.

ALCOHOL COMBUSTION SYSTEM TO GENERATE

CO₂ PRODUCTION AND O₂ CONSUMPTION

A 60-mL syringe (Becton Dickinson & Co., Franklin Lakes, NJ, USA), installed in a precision syringe pump (Syringe pump A-99, Razel Scientific Instruments Inc., Stamford, CT, USA), delivered an adjustable, metered flow of ethanol to the burner assembly inside the metabolic chamber. We designed and constructed a custom alcohol burner. The syringe pump was connected to a 20-cm 1/8" outer diameter copper tube, which terminated in an elbow brass fitting (Swagelok Co. Cleveland, OH, USA). This fitting held the 1/8" cotton wick (PM Research Inc. Wellsville, NY, USA). The alcohol was pure ethanol (Gold Shield Alcohol, proof 200, Hayward, CA, USA). The combustion of ethanol^{10,19} is given by:

so that the respiratory quotient, RQ ($\dot{V}\text{CO}_2/\dot{V}\text{O}_2$) is 2/3 (0.667).

For a given minute volume delivery (mL·min⁻¹) of liquid ethanol (Q),

$$\text{moles}_{\text{ethanol}}/\text{min} = \rho \cdot Q / \text{MW}, \quad \text{Equation 5}$$

where ρ is the density of ethanol (0.7893 g/cm³) at syringe T (25°C) and MW is the molecular weight of ethanol (46.069 g·mole⁻¹). Since the molar volume of a gas (Avogadro's law) is 22,414 mL STPD (standard temperature and pressure, dry),

$$\dot{V}\text{CO}_2 \text{ (mL}\cdot\text{min}^{-1}, \text{STPD)} = \text{moles}_{\text{ethanol}} / \text{min} \cdot 2 \cdot 22,414, \text{ and} \quad \text{Equation 6}$$

$$\dot{V}\text{O}_2 \text{ (mL}\cdot\text{min}^{-1}, \text{STPD)} = \text{moles}_{\text{ethanol}} / \text{min} \cdot 3 \cdot 22,414 \quad \text{Equation 7}$$

Table I displays the five infusion rates of ethanol into the combustion chamber and the corresponding stoichiometric generation of $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$. The liquid ethanol infusion flow rates for combustion in the metabolic chamber were chosen so that resultant $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$ would span the physiological range of adults and children (> 25 kg body weight).

FAST-RESPONSE AIRWAY HUMIDITY AND TEMPERATURE SENSOR

To allow conversion of airway gas flows to STPD values,^{10,15} we developed a fast response humidity and temperature (T) sensor^{20,21} (U.S. Patent #6,014,890),^A which was attached to the airway opening of the mechanical lung (Figure 1). Two tiny thermometers (copper and constantan type T thermocouples, Omega Engineering, Inc., Stamford, CT, USA) were mounted in a standard anesthesia adapter (T adapter, Datex-Ohmeda, Milwaukee, WI, USA). A

TABLE I Precise generation of CO₂ production ($\dot{V}\text{CO}_2$) and O₂ consumption ($\dot{V}\text{O}_2$) at five infusion rates of liquid ethanol (C₂H₆O) into the combustion metabolic chamber

Ethanol		Stoichiometry	
Q (mL·min ⁻¹)	m (g·min ⁻¹)	$\dot{V}\text{CO}_2$ (mL·min ⁻¹ STPD)	$\dot{V}\text{O}_2$ (mL·min ⁻¹ STPD)
0.079	0.062	59.9	89.8
0.167	0.132	128.3	192.5
0.245	0.193	188.2	282.3
0.323	0.255	248.1	372.1
0.412	0.325	316.6	474.8

The ethanol volumetric infusion rates for combustion in the metabolic chamber were chosen so that resultant $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$ would span the physiological range of adults and children (> 25 kg body weight). Q = volumetric infusion of liquid ethanol; m = mass of ethanol per min; STPD = standard temperature and pressure, dry.

thermocouple is the junction of two dissimilar metals, which generates a small voltage potential as a function of junction T. One thermocouple was constantly wetted by a special wicking system^A (wet T). Airway gas T was measured by dry T. Humidity was measured by psychrometry,²² where dry gas causes evaporative cooling to decrease wet T below dry T. Each thermocouple was connected to a separate isolated linearized thermocouple amplifier equipped with cold-junction compensation (model 5B47 amplifier, energized in a 5B08 8-channel back-plane, Analog Devices, Norwood, MA, USA). The thermocouple voltage potentials were amplified about 5,000 times.

DATA COLLECTION

The anesthesia monitor (Capnomac Ultima, Datex Medical Instruments) was connected to the pneumotachometer cuvette through dual-lumen pressure tubing. The monitor sampling line was connected to the bymixer sampling port (200 mL·min⁻¹) (Figures 1 and 2). FO₂ and FCO₂ were measured by paramagnetic and infrared principles, respectively. The Capnomac monitor routes the gas sample through water permeable tubing (Nafion®) before entering the measurement cuvettes (CO₂ and O₂). Thus, the gas samples are always measured at ambient room humidity. Performance of the water permeable tubing was tested by sampling dry room air compared with gas over open boiling water; there was no change in measured gas fractions. Temperature in the measurement cuvettes was not considered because gas fractions do not change with T.¹⁰

All signals were continuously captured (100 Hz) by analogue-to-digital acquisition PC card (DAQcard 700, National instruments, Austin, TX, USA) installed in a notebook computer (Inspiron 3800, Dell Computer Corp., Austin, TX, USA). The operating system was Windows 2000 Professional (Microsoft Corp., Redmond, WA, USA). The digital data acquisition system was driven by a custom program (Delphi Pascal, Borland International, Scotts Valley, CA, USA) written by our computer support specialist (David Chien) and one author (P.H.B.).

EXPERIMENTAL PROTOCOL

At each ethanol infusion rate, we waited about 15 min for steady state, signalled by steady values of end-tidal PCO₂ (PETCO₂) and the FIO₂-FETO₂ relationship. Then,

the measurement sequence was conducted, consisting of the digital sampling of the following parameters for one minute: airway flow, pressure, dry T, and wet T, and bymixer F_ECO₂, F_EO₂, FICO₂, and FIO₂. For each experiment, this procedure was repeated at each of the five infusion rates of ethanol (Table I). The entire experiment was repeated on four different days.

We conducted two additional separate procedures. First, to test the need for an inspired limb bymixer in the circle circuit ventilation of the metabolic lung simulator, the inspired limb FO₂ (without a bymixer) was compared to the value sampled from the inspired limb bymixer. Second, to test that gas flow did not cross the circle circuit Y-adapter, the pneumotachometer was placed in the inspired limb to confirm absence of inspired limb $\dot{V}$ during expiration and in the expired limb to confirm absence of expired limb $\dot{V}$ during inspiration.

DATA ANALYSIS¹⁰

Airway $\dot{V}$ O₂ and $\dot{V}$ CO₂ were calculated by equations 2 and 3, respectively. Since the gas monitor does not measure nitrogen concentration directly, FN₂ was given by:

$$FN_2 = 1 - FCO_2 - FO_2 \quad \text{Equation 8}$$

Exhaled ventilation was calculated by:

$$\dot{V}_E = \left\{ \sum_1^n \left(\int_{BE}^{EE} \dot{V}(t) dt \right)_n \right\} \cdot n^{-1} \cdot f \quad \text{Equation 9}$$

where BE and EE was begin- and end-expiration respectively of each breath, n; dt was the digital sampling period (1/100 Hz = 0.01 sec); and f was the respiratory frequency.

Conversion to STPD conditions¹⁵ proceeded by:

$$\dot{V}_{STPD} = \dot{V}_{ATPS} \cdot ([P_{TOT} - P_{H_2O}] / P_{TOT}) \cdot (273 / [273 + T]) \cdot (P_{TOT} / 760) \quad \text{Equation 10}$$

where $\dot{V}_{ATPS}$ was the airway flow measured at ambient temperature, pressure, and saturation conditions (ATPS), P_{TOT} was ambient barometric pressure plus airway pressure, and P_{H_2O} was the water vapour partial pressure determined by psychrometry²² from the airway humidity and T sensor.^A Equation 10 converts ATPS to STPD¹⁵ by removing volume expansion due to water vapour (second term on right side of equation), by removing volume expansion due to thermal change above 0°C (273°K) (third term), and by removing volume change due to a pressure variation from 760 mmHg (fourth term).

We developed a computer program to automate data analysis (Excel spreadsheet, Microsoft Corp., Redmond, WA, USA). If required, airway flow was

A Breen PH. Fast response humidity and temperature sensor device. United States Patent, Jan. 18, 2000; Number 6,014,890: 14 pages.

processed by a moving average filter. The algorithms defined negative values of flow as inspiration and positive values as expiration. The computer routines also identified the begin time of the first inspiration and the end time of the last expiration. Then, expired volume was determined by the integration of expired flow with respect to time. Using simultaneous measurements of airway T and relative humidity, and inspired and expired gas fraction measurements from the bymixers, the program automatically converted gas volumes to STPD conditions, and then calculated $\dot{V}O_2$ and $\dot{V}CO_2$.

STATISTICAL ANALYSIS

Airway $\dot{V}CO_2$ and $\dot{V}O_2$ were compared to the stoichiometric values generated by ethanol combustion by least squares linear regression (slope, Y-intercept, and coefficient of determination, R^2) and by the limits of agreement (LOA) technique described by Bland and Altman.^{23–25} Computer programs were used for statistical testing (Medcalc, Medcalc Software, Mariakerke, Belgium),^B and graphical presentation (SigmaPlot 8.0, SPSS).

Results

For each experiment, Figure 3 displays linear regression²⁶ of the bymixer-airway flow measurements of $\dot{V}CO_2$ (open circles and dotted lines) and $\dot{V}O_2$ (solid circles and lines) versus the stoichiometric values generated by metered ethanol combustion. When all data points were analyzed together by linear regression, for $\dot{V}CO_2$, slope was 1.02, Y-intercept was -5.31, and R^2 was 0.998. For $\dot{V}O_2$, slope was 1.05, Y-intercept was -4.34, and R^2 was 0.993. While the correlation between the airway and stoichiometric values for both $\dot{V}CO_2$ and $\dot{V}O_2$ were excellent in each experiment, inspection of the linear regression analysis suggested a relatively small proportionality factor (i.e., slope, m , was not unity) in the airway measurement of both $\dot{V}CO_2$ and $\dot{V}O_2$.

The LOA analysis^{23,25} (Figure 4) demonstrated good agreement between the airway measured values and the stoichiometric values generated by ethanol combustion. Limits of agreement (mean $\pm$ 1.96 SD) for $\dot{V}CO_2$ were -0.70 ± 9.15 mL·min⁻¹, where 95% of the points (19 out of 20 trials) were bounded by those limits (upper panel, Figure 4). However, as average $\dot{V}CO_2$ increased along the X-axis, the difference between the measurements reflected a proportionality

FIGURE 3 Linear regression of bymixer-airway flow measurements of $\dot{V}CO_2$ (open circles and dotted lines) and $\dot{V}O_2$ (solid circles and lines) vs the stoichiometric values generated by metered ethanol combustion. Each panel is a separate experiment. m = slope; b = Y-intercept; R^2 = coefficient of determination.

factor (see Figure 3, dotted linear regression lines) that shifted the mean and LOA in a positive direction along the Y-axis. Thus, at lower $\dot{V}CO_2$, the airway measurement tended to be less than the reference value. At higher $\dot{V}CO_2$, the airway measurement tended to be higher than the reference value. In a similar analysis for $\dot{V}O_2$ (lower panel), LOA were 8.79 ± 25.34 mL·min⁻¹. Similar to $\dot{V}CO_2$, as the average value of $\dot{V}O_2$ increased along the X-axis, there was a proportional increase in the mean and LOA in a positive direction (see Figure 3, solid linear regression lines).

To account for these proportionality errors in the airway measurements, the upper panel of Figure 5 plotted the ratio²⁴ of the airway measurement of $\dot{V}CO_2$ to the stoichiometric value, vs the average of both values. The ratio LOA (mean $\pm$ 1.96 SD) for $\dot{V}CO_2$ were 0.988 ± 0.072 or, expressed as a percentage, $-1.2 \pm 7.2\%$, where 95% of all points lay within these limits. In a similar analysis for $\dot{V}O_2$ (Figure 5, lower panel), ratio LOA were 1.025 ± 0.098 or, expressed as a percentage, $2.5 \pm 9.8\%$.

The average ($\pm$ 1.96 SD) percent error for airway $\dot{V}CO_2$ (compared to the stoichiometric value) was $-1.17 \pm 7.19\%$ (Table II). The average ($\pm$ 1.96 SD) percent error for airway $\dot{V}O_2$ was $2.49 \pm 9.80\%$. Average R was 0.643 ± 0.016 . If inspired and expired gas flows were not converted to STPD conditions, the average percent error (mean $\pm$ 1.96 SD) in airway

B MedCalc manual. MedCalc Software, Mariakerke, Belgium; 2002.

FIGURE 4 *Top panel:* Bland-Altman limits of agreement (LOA) analysis for carbon dioxide elimination ($\dot{V}\text{CO}_2$). The difference between the bymixer-airway flow measurement of $\dot{V}\text{CO}_2$ and the value generated by the metabolic lung simulator was plotted against the average of the two values. The mean $\pm$ 1.96 SD LOA for $\dot{V}\text{CO}_2$ were $-0.70 \pm 9.15 \text{ mL}\cdot\text{min}^{-1}$. *Bottom panel:* in a similar analysis for oxygen uptake ($\dot{V}\text{O}_2$), LOA were $8.79 \pm 25.34 \text{ mL}\cdot\text{min}^{-1}$. The LOA bound 95% of all points. The linear regression line of the plotted points shows a proportional error for both $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$.

measurements of $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$ significantly increased ($5.75 \pm 6.90\%$ and $10.55 \pm 9.04\%$, respectively).

Figure 6 displays the importance of the bymixer in the inspired limb of the anesthesia circle circuit. The *upper panel* depicts airway opening gas flow and inspired limb FO_2 during ventilation of the metabolic lung simulator with the anesthesia circle circuit. The inspired limb FO_2 displayed significant fluctuations (amplitude of 3.52%). In the *lower panel*, with a clini-

FIGURE 5 *Top panel:* the Bland-Altman ratio analysis for carbon dioxide elimination ($\dot{V}\text{CO}_2$). The ratio of the bymixer-airway flow measurement of $\dot{V}\text{CO}_2$ and the value generated by the metabolic lung simulator was plotted against the average of the two values. Ratio limits of agreement (LOA) (mean $\pm$ 1.96 SD) for $\dot{V}\text{CO}_2$ were 0.988 ± 0.072 . *Bottom panel:* similar ratio LOA analysis for oxygen uptake ($\dot{V}\text{O}_2$) was 1.025 ± 0.098 .

cal bymixer interposed in the inspiratory limb of the circle circuit, bymixer FO_2 had minimal variation over inspiration.

In another procedure, when positioned in the inspired limb, the pneumotachometer measured 0 inhaled $\dot{V}$ during expiration. Similarly, the pneumotachometer measured 0 $\dot{V}$ in the expired limb during inspiration.

Discussion

We have developed a measurement of airway opening oxygen uptake ($\dot{V}\text{O}_2$) and carbon dioxide elimination

FIGURE 6 Importance of the bymixer in the inspired limb of the anesthesia circle circuit. *Upper panel:* airway opening gas flow and inspired limb oxygen fraction (FO_2 , thin line) during ventilation of the metabolic lung simulator with the anesthesia circle circuit. Five respiratory cycles are displayed. Negative airway flow was inspiration and positive airway flow was expiration. The inspired limb FO_2 displayed significant fluctuations (amplitude of 3.52%). *Lower panel:* with the new clinical bymixer interposed in the inspiratory limb of the circle circuit, bymixer FO_2 (thin line) had minimal variation over inspiration.

($\dot{V}\text{CO}_2$) in the anesthesia circle ventilation circuit using the new clinical bymixer and a standard clinical airway opening flowmeter. This bymixer-flow measurement was validated in the circle circuit ventilation of the new metabolic lung simulator. The metabolic lung simulator generated a precise stoichiometric range of O_2 consumption and CO_2 production by the combustion of metered liquid ethanol. The Bland-Altman ratio LOA for $\dot{V}\text{CO}_2$ (mean ± 1.96 -SD) were 0.988 ± 0.072 and for $\dot{V}\text{O}_2$ were 1.025 ± 0.098 , corresponding to

percent errors of $1.2 \pm 7.2\%$ for $\dot{V}\text{CO}_2$ and $2.5 \pm 9.8\%$ for $\dot{V}\text{O}_2$. These values correlated well with the average error (± 1.96 SD) of each measurement (Table II). The error range for $\dot{V}\text{O}_2$ was slightly larger than the error for $\dot{V}\text{CO}_2$ because $\dot{V}\text{O}_2$ depends on measurements of both inspired and expired gas fractions, while $\dot{V}\text{CO}_2$ depends mostly on expired gas fractions.⁸

While the Bland-Altman LOA analysis²³⁻²⁵ is the most accepted method to assess the accuracy of bymixer-flow airway measurements of indirect calorimetry, additional information can be found by inspection of the individual linear regression plot for each experiment (Figure 3). Airway bymixer-flow measurements of $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ displayed tight correlation to the values generated by the metabolic lung simulator. However, the strong correlation of $\dot{V}\text{O}_2$ in each experiment (coefficient of determination, R^2 , near unity) was slightly higher than the values of R^2 when all data were pooled, because the slope and Y-intercept varied slightly from experiment to experiment. In contrast to $\dot{V}\text{CO}_2$, $\dot{V}\text{O}_2$ is more sensitive to inter-experiment variability due to its dependence on inspired as well as expired gas fractions.

In Table II, note the precise determination of the respiratory exchange ratio, R (0.643 ± 0.016). R is a sensitive parameter because it is the ratio of the two airway measurements ($\dot{V}\text{CO}_2/\dot{V}\text{O}_2$). This high accuracy and precision of measured airway R presents a reliable indicator for metabolic monitoring and clinical decisions.¹¹ R was offset slightly from the expected ethanol combustion stoichiometric value of 0.667 because of the proportionality effects present in the measurements of $\dot{V}\text{CO}_2$ and $\dot{V}\text{O}_2$ (Figures 3 and 4).

Without STPD correction,¹⁰ the average error increased about fourfold. To provide data for conversion of gas flows to STPD conditions, we utilized our fast response airway sensor^A to provide continuous airway opening measurements of humidity and temperature.²¹

We chose to perform this study of the bymixer-flow measurements of $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ using an FIO_2 of 60% ($\text{FIN}_2 = 40\%$) since most patients undergoing surgery and anesthesia are ventilated with oxygen fractions at or below this level. The accuracy of the bymixer-airway flow measurements of indirect calorimetry should be even better at lower FIO_2 , because the fraction of nitrogen increases in the respiratory gas (equation 2). Similar to commercial monitors, our bymixer-flow measurement system invokes a clinical gas analysis monitor that does not measure FN_2 . Instead FN_2 is calculated by subtracting the other gas fractions from unity (equation 8). If available, a mass spectrometer²⁷ can directly measure FN_2 and potentially further

TABLE II Bymixer-airway flow measurements of CO₂ elimination ($\dot{V}_{CO_2}$) and O₂ uptake ($\dot{V}_{O_2}$), using exhaled flow and bymixer gas fractions, compared to the stoichiometric reference values of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, generated by five infusion rates of ethanol into the combustion metabolic chamber. Four experiments (Expt), on separate days, are shown.

Expt	$\dot{V}_{CO_2}$ (mL·min ⁻¹)			$\dot{V}_{O_2}$ (mL·min ⁻¹)			R
	Stoichiometry	Airway	% error	Stoichiometry	Airway	% error	
1	316.5	320.7	1.32	474.8	496.2	4.50	0.646
	248.1	246.1	-0.79	372.1	374.6	0.65	0.657
	188.2	197.8	5.07	282.3	314.3	11.34	0.629
	128.3	132.4	3.15	192.5	211.9	10.06	0.625
	85.6	84.6	-1.16	128.3	134.1	4.48	0.631
2	316.5	319.3	0.87	474.8	487.1	2.59	0.655
	248.1	250.6	1.02	372.1	388.5	4.40	0.645
	188.2	192.6	2.35	282.3	297.9	5.52	0.647
	128.3	123.3	-3.95	192.5	188.7	-1.99	0.653
	85.6	81.5	-4.70	128.3	129.3	0.73	0.631
3	316.5	319.0	0.76	474.8	512.3	7.90	0.623
	248.1	241.1	-2.83	372.1	367.1	-1.35	0.657
	188.2	189.6	0.75	282.3	287.4	1.81	0.660
	128.3	123.0	-4.19	192.5	186.9	-2.89	0.658
	85.6	79.1	-7.57	128.3	119.2	-7.10	0.663
4	316.5	314.6	-0.60	474.8	476.7	0.40	0.660
	248.1	247.5	-0.26	372.1	379.2	1.88	0.653
	188.2	187.9	-0.15	282.3	296.4	4.99	0.634
	128.3	125.9	-1.91	192.5	208.5	8.30	0.604
	85.6	76.5	-10.53	128.3	120.0	-6.51	0.638
		<i>Mean</i>	<i>-1.17</i>		<i>Mean</i>	<i>2.49</i>	<i>0.643</i>
		$\pm$ SD	$\pm$ 3.67		$\pm$ SD	$\pm$ 5.00	$\pm$ 0.016
		$\pm$ 1.96SD	$\pm$ 7.19		$\pm$ 1.96SD	$\pm$ 9.80	

For $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, % error = 100 (airway - stoichiometry)/stoichiometry; R = respiratory exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$).

enhance the accuracy of the measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$.

This bench study establishes that the bymixer-airway flow measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ in the anesthesia circle circuit are accurate and precise. The anesthesia circle ventilation circuit has unique design characteristics, which pose three potential problems for the bymixer-flow measurement of indirect calorimetry. First, each exhaled gas volume becomes part of the next inspired volume. Hence, F_{IO_2} may vary over the time of inspiration. The upper panel of Figure 6 demonstrates that F_{IO_2} does indeed vary during inspiration. Accordingly, the inspired limb bymixer was required to provide a flow-averaged value of F_{IO_2} , in addition to the separate expired limb bymixer which provided flow-averaged values of F_{EO_2} and $F_{\bar{E}O_2}$.

Second, the configuration of the anesthesia circle ventilation circuit must not allow gas flow across the circuit Y-piece during the respiratory cycle. Figure 1 displays the standard arrangement of the anesthesia circle circuit used in all contemporary anesthesia systems.¹² Beginning with expiration at the airway opening, gas flows through the Y-adapter, expiratory limb and one-way valve, bag/ventilator/exhaust gas

system, CO₂ absorber, FGF inlet adapter, inspiratory one-way valve, and inspiratory limb. Separate flow tests in our circle circuit (Narkomed 2A, N.A. Dräger, Germany) confirmed absence of gas flow across the Y-adapter. The circle circuit has hidden elegance. At the end of expiration (when expired flow has ceased), one might erroneously assume that FGF will begin to flow around the circuit (in the direction of the one-way valves) and *across* the Y-adapter. However, at the end of expiration, FGF into the circle circuit pressurizes *equally* the inspired and expired limbs so that there is no pressure gradient for gas flow around the circle circuit. Instead, FGF flows *retrograde* in the circuit through the CO₂ absorber to exit through the exhaust port. Beware of older implementations of the circle circuit²⁸ which can cause gas flow across the Y-adapter. In an effort to reduce dead space, the FGF inlet has previously been placed on the patient side of the inspiratory one-way valve,²⁹ causing, towards the end of expiration, FGF to flow around the circle circuit. Alternatively, other older anesthesia circuit systems have incorporated a circulator³⁰ or small fan to continuously circulate gas around the circle circuit.

Third, the bymixer-airway flow measurement in the anesthesia circle circuit requires competent one-way valves. An incompetent inspiratory valve would allow the retrograde flow of exhaled gas into the inspired limb during exhalation¹⁷ and corrupt the measured inspired gas concentrations. An incompetent expiratory valve would allow, during inspiration, retrograde flow through the expired limb with contamination of the expired gas fractions. Of course, incompetent inspiratory or expiratory one-way valves also cause rebreathing of exhaled gas.

During anesthesia, there are other non-invasive strategies to measure $\dot{V}O_2$ and $\dot{V}CO_2$ at the airway opening. During steady state conditions, FGF of oxygen can be decreased to the value ($\dot{V}O_2$) which maintains a constant end-expired position of the ascending ventilating bellows (closed circuit anesthesia) (Figure 1).¹³ However, this volumetric method is impractical during anesthesia because it requires complete CO_2 absorption, a precise O_2 flowmeter, and absolute absence of gas leaks in the anesthesia machine and circuit. Furthermore, the volumetric methodology is lengthy and rather cumbersome, repeatability is slow, and $\dot{V}CO_2$ cannot be measured. Carbon dioxide elimination must be estimated by assuming a value for R ($\dot{V}CO_2 = R \cdot \dot{V}O_2$).¹⁶

Another approach to the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ during anesthesia is the online multiplication and integration of continuous digital measurements of gas flow and gas fractions at the airway opening³¹ (M-CAiOVX module, Datex-Ohmeda, Instrumentarium Corporation, Helsinki, Finland). After sophisticated temporal response correction, the digital measurements of gas flow, F_{CO_2} , and F_{O_2} are processed to yield calculated values of $F\bar{E}CO_2$ and $F\bar{E}O_2$. Then, the Haldane transformation is utilized to generate frequently updated determinations of $\dot{V}CO_2$ and $\dot{V}O_2$. The M-CAiOVX module requires only one adapter at the airway opening and has the potential for breath-to-breath determinations of $\dot{V}O_2$ and $\dot{V}CO_2$. However, the technology is complicated and requires sensitive response correction of the measurements of gas flow and concentration. The device is expensive and has not been rigorously tested during anesthesia ventilation with the circle circuit.

In contrast, the clinical bymixer (a simple and inexpensive device), when mated with any clinical anesthesia flowmeter and gas analyzer, provides accurate airway determinations of $\dot{V}O_2$ and $\dot{V}CO_2$. The dynamic response of the bymixer is about $\frac{1}{4}$ min, which allows updated measurements every $\frac{3}{4}$ min. This response time of the bymixer-airway flow measurement of indirect calorimetry should be adequate for most non-

steady state perturbations (e.g., abrupt decrease in cardiac output) or changes in tissue metabolism (e.g., onset of anaerobic metabolism).

Certain remnant gases can accumulate in the anesthesia circuit, particularly when using low FGF and during long procedures.²⁸ These remnant gases include carbon monoxide, acetone, methane, hydrogen and ethanol and can accumulate to 1% of the total gas volume of the anesthesia circuit. Any accumulation of remnant gas would result in a lower value for both inspired and expired N_2 (equation 8). We used our computer program, which automated data analysis of $\dot{V}CO_2$ and $\dot{V}O_2$ using equations 1–10, to examine the effect of 1% remnant gas in the circuit. In four random data sets, the influence of 1% remnant gas on $\dot{V}O_2$ was less than 0.7%. Any presence of remnant gas does not affect $\dot{V}CO_2$, because there is negligible CO_2 in inspired gas (equation 3).

The bymixer-flow measurement of $\dot{V}CO_2$ and $\dot{V}O_2$ by airway indirect calorimetry may help detect and manage critical events during anesthesia^{5–10} and onset of anaerobic metabolism.^{6,11} Further clinical studies are required to delineate the clinical significance of these monitoring technologies during anesthesia and surgery, and how they augment or compare with current monitoring modalities.

Because anesthesia ventilation systems typically employ a circle ventilating circuit, the usual collection of exhaust gas, for measurement of mixed expired gas fractions required for the calculation of $\dot{V}O_2$ and $\dot{V}CO_2$, is not available. We describe, for the first time, the positioning of the mechanical inline mixing chamber (bymixer) in the expiratory and inspiratory limbs of the anesthesia circle circuit to allow accurate measurements of $\dot{V}O_2$ and $\dot{V}CO_2$. The bymixer is compact, lightweight, disposable, inexpensive, and does not collect condensed moisture or secretions.⁵ Since the mixing chamber channel reunites downstream with the main flow, no gas is lost in the measurement process, supporting the use of low FGF anesthesia.

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