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Measurement of Oxygen Uptake and Carbon Dioxide Elimination Using the Bymixer

Validation in a Metabolic Lung Simulator

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Background: **The authors have developed a new clinical bymixer that bypasses a constant fraction of gas flow through a mixing arm. A separate bymixer was interposed in the expiratory and inspiratory limbs of the ventilation circuit to measure mixed gas fractions. By utilizing nitrogen conservation, the clinical bymixer allows the determination of airway carbon dioxide elimination ($\dot{V}_{CO_2}$) and oxygen uptake ($\dot{V}_{O_2}$), whenever basic expired flow and gas monitoring measurements are used for the patient. Neither an expiratory exhaust gas collection bag nor expensive, complex equipment are needed. This study tested the accuracy of airway bymixer-flow measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ in a new bench apparatus.**

Methods: **The authors compared airway bymixer-flow measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ over a range of reference values generated by ethanol combustion in a new metabolic lung simulator, which was ventilated by a volume-cycled respirator. An airway humidity and temperature sensor permitted standard temperature and pressure, dry, correction of airway $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$.**

Results: **Bymixer-flow airway measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ correlated closely (R^2 = 0.999 and 0.998, respectively) with the stoichiometric values generated by ethanol combustion. Limits of agreement for $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were 0.1 ± 4.7 and 1.1 ± 5.7%, respectively. The average (± SD) percent error for airway $\dot{V}_{CO_2}$ (compared with the stoichiometric value) was 0.1 ± 2.4%. The same error for airway $\dot{V}_{O_2}$ was 1.1 ± 2.9%.**

Conclusions: **The new clinical bymixer, plus basic expired flow and gas fraction measurements, generated clinically accurate determinations of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$. These measurements are helpful in the assessment of metabolic gas exchange in the critical care unit. In contrast to using the gas collection bag or complex metabolic monitor, the bymixer should measure mixed gas concentrations in the inspired or expired limb of the common anesthesia circle ventilation circuit.**

INDIRECT calorimetry, the measurement of airway carbon dioxide elimination ($\dot{V}_{CO_2}$), airway oxygen uptake $\dot{V}_{O_2}$), and the respiratory quotient (RQ = $\dot{V}_{CO_2}/\dot{V}_{O_2}$), is used for cardiopulmonary exercise testing[1] and the determination of noninvasive metabolic gas exchange in the intensive care unit.[2,3] Indirect calorimetry has a wide range of clinical applications in critical care medicine, including the assessment of metabolic expenditure (resting energy expenditure) and the titration of nutritional support.[2] In the normal condition, where carbon dioxide is absent from inspired gas,

$$\dot{V}_{CO_2} = \dot{V}_E \cdot F\bar{E}_{CO_2}, \quad (1)$$

where $\dot{V}_E$ is the expired ventilation and $F\bar{E}_{CO_2}$ is the mixed expired carbon dioxide fraction. Oxygen uptake is given by:

$$\dot{V}_{O_2} = \dot{V}_I \cdot F_{IO_2} - \dot{V}_E \cdot F\bar{E}_{O_2}, \quad (2)$$

where I denotes inspiration. Standard indirect calorimetry methodology invokes the principle of conservation of the inert gas nitrogen during the steady state condition (Haldane transformation),[4,5] where $\dot{V}_I \cdot F_{IN_2} = \dot{V}_E \cdot F\bar{E}_{2}$. Substitution into equation 2 yields:

$$\dot{V}_{O_2} = \dot{V}_E \, (F_{IO_2} \cdot F\bar{E}N_2/F_{IN_2} - F_{EO_2}). \quad (3)$$

Accordingly, $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ can be determined from measurements of minute ventilation ($\dot{V}_E$) and mixed inspired and expired gas fractions. Hence, the Haldane transformation compensates for flow measurement inaccuracies between inspiration and expiration.

Mixed expired gas fractions are classically measured in a collection bag (Douglas bag) attached to the expiratory exhaust port of the ventilator,[1,6] but the apparatus is bulky, and the procedure is time consuming and cannot be quickly repeated. In critical care medicine, commercial metabolic monitors[4] attach directly onto the exhaust gas port of the ventilator (*e.g.*, Datex Deltatrac II Metabolic Monitor; Datex Instrumentarium, Helsinki, Finland).[7,8]

We have developed a new clinical bymixer[9] (fig. 1), an inline, compact, disposable mixing device that is interposed in the expiratory and inspiratory limbs of the ventilator circuit. The bymixer bypasses a constant fraction of gas flow through a mixing arm. A gas monitor continuously samples gas from the bymixer to measure mixed gas fractions. Accordingly, the clinical bymixer allows the determination of indirect calorimetry whenever basic expired flow and gas monitoring measurements are in use for the patient,[10] without the need for expensive, dedicated, and complex equipment. Furthermore, in contrast to the gas collection bag or metabolic monitor, the bymixer is also able to measure gas frac-

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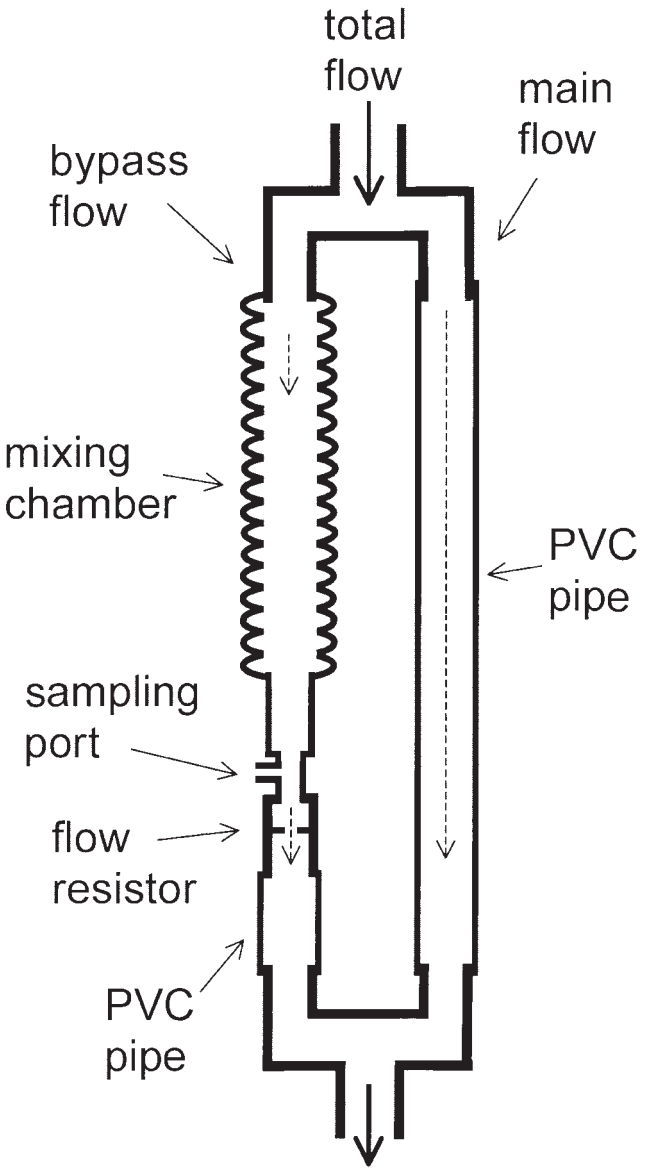

Fig. 1. New clinical bymixer.[9] The resistor determines the constant fraction of total flow that bypasses through the mixing chamber ($\dot{V}_{BYPASS}$). The volume of the mixing chamber (V_{BYPASS}) can be adjusted by changing the length of corrugated tube. The mixing chamber tube is coiled (not shown) to reduce total length of the bymixer. A sidestream gas analysis monitor aspirates flow-averaged (mixed) gas from the sampling port. The time constant or responsiveness of the bymixer to a change in input gas concentration is given by τ (= $V_{BYPASS}/\dot{V}_{BYPASS}$). Hence, decreasing V_{BYPASS} improves bymixer response but with potential for incomplete gas mixing. In this study, the volume of the mixing arm was 200 ml.

tions in the inspired limb of the ventilation circuit. Thus, the bymixer can measure mixed gas concentrations in both limbs of the anesthesia circle circuit. Several authors[4,11] have indicated the need for an inspiratory limb bymixer because of an unstable inspired oxygen fraction, especially in a semiclosed system with low input of fresh gas flow. Despite the fact we used an open-circuit ventilator in this study, we decided to use an inspiratory limb bymixer to eliminate any chance of error originating from unstable fractional inspired oxygen (F_{IO_2}) and to validate its use in the $\dot{V}_{O_2}$ measurement.

In this study, we tested how the new clinical bymixer, along with a standard clinical flowmeter and gas monitor, can measure $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$. We invoked a specially designed metabolic lung simulator (fig. 2), which was an extension from previous work.[12] Complete combustion of metered ethanol provided accurate reference carbon dioxide production and oxygen consumption. A rapid response airway sensor of relative humidity (RH) and temperature (T)[13] was required and used to convert gas volumes to standard temperature and pressure, dry (STPD) condition.

Materials and Methods

New Clinical Bymixer

To measure mixed gas fractions,[14] we developed a mechanical clinical bymixer[9] (patent pending, applied for by Peter H. Breen) (fig. 1), which *by*passes a constant portion of the main flow through the *mix*ing chamber. The main flow channel was constructed of a 24-cm length of standard ¾-in polyvinyl chloride pipe (22 mm ID). The bypass channel was composed of a length of expandable–collapsible pediatric anesthesia circuit tubing (15 mm ID, Expandoflex; Cleveland Tubing Inc., Cleveland, TN). The adjustable tubing was connected, in series, to a sampling port adapter (Datex-Engstrom Division, Instrumentarium Corp., Helsinki, Finland), a flow resistor, and a 12-cm length of standard ¾-in polyvinyl chloride tubing. The flow resistor was constructed by placing a plastic cap with a 4-mm hole (NAS-820-10; Niagra Plastics, Erie, PA) inside a connector (Multi Adapter; Hudson RCI, Temecula, CA; 15 mm ID, 22 mm OD). 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. The volume of the bypass channel from the sampling port to the downstream Y connector was 53 ml. The main flow and bypass flow channels were connected at each end by identical Y connectors (supplied with standard anesthesia circle circuits). With coiling of the mixing arm, the bymixer length was 37 cm. The average width was 8 cm, and the weight was 149 g. The ratio of bypass flow to total flow was 1:9.[9]

Experimental Setup of Metabolic Lung Simulator

Experimental setup of the metabolic lung simulator is shown in figure 2. The mechanical lung (Dual Adult TTL, model 1600; Michigan Instruments, Inc., Grand Rapids, MI) was connected by a circular circuit to an airtight, rigid chamber (5.7 l pressure cooker). Both the pressure-relief valve and the emergency valve of the cooker were sealed. The pressure cooker was glued to the bottom of a large, flat, open container. Tap water constantly flowed

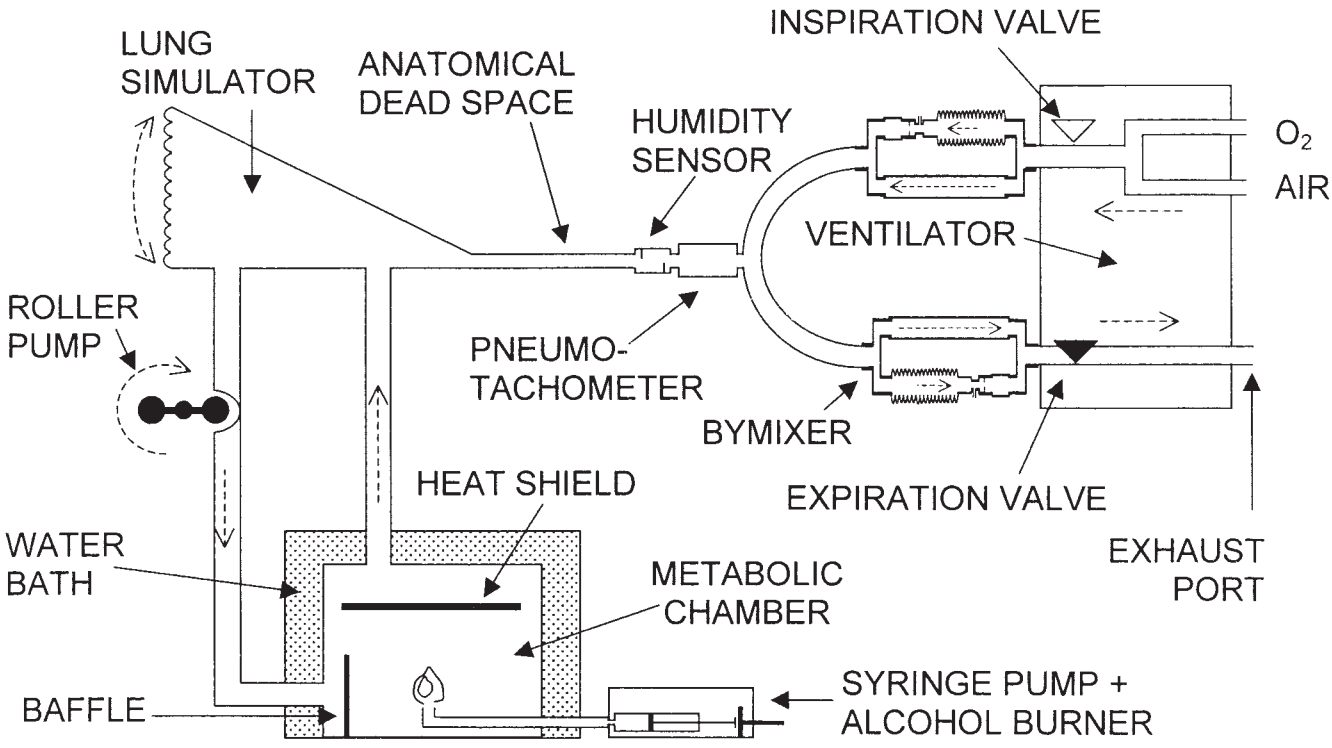

Fig. 2. Metabolic lung simulator. The mechanical lung was connected to the rigid wall metabolic chamber through a circular circuit. An occlusive roller pump drove gas flow through the circuit at 5 l/min. A second roller pump (not shown) helped to return gas from the metabolic chamber to the mechanical lung. This dual-pump design protected the metabolic chamber from ventilatory pressure fluctuation to ensure stable alcohol combustion. A gauge sensed pressure in the metabolic chamber to facilitate flow equilibration of the two pumps. A precision syringe pump delivered an adjustable, metered flow of ethanol to the burner assembly inside the metabolic chamber. The metabolic chamber was maintained at constant temperature in a cooling water bath. The open circuit ventilator inspired and expired limbs joined at the Y junction. A bymixer was interposed in each limb of the ventilation circuit. In order, the Y junction was connected to the pneumotachometer adapter, the humidity and temperature sensor, and the mechanical lung. The ventilator is depicted during inspiration.

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 pressure cooker. An occlusive roller pump (15-mm-ID tubing; Precision Blood Pump; COBE Perfusion System, Lakewood, CO) generated constant gas flow (5 l/min) between the metabolic chamber and the lung simulator. A second roller pump (not shown) helped to return gas from the metabolic chamber to the mechanical lung. This dual-pump design protected the metabolic chamber from ventilatory pressure fluctuation to ensure stable alcohol combustion. A pressure gauge, connected to the metabolic chamber, facilitated flow equilibration between the two pumps.

The inspired and expired limbs of the open circuit ventilator (Servo Ventilator 900C; Siemens AB, Solna, Sweden) joined at the Y junction. A bymixer was interposed in each limb of the ventilation circuit. In order, the Y junction was connected to the pneumotachometer adapter (Capnomac Ultima; Datex Medical Instruments, Instrumentarium Corp.), the humidity and temperature sensor, and a 50-cm tube leading to the mechanical lung. These latter three components composed the anatomical dead space of the mechanical lung, determined by the Bohr calculation to be 150 ml. The end-expiratory volume of the mechanical lung was 920 ml. The ventilator is depicted during inspiration. The lung simulator was ventilated with 60% dry oxygen in nitrogen. At each level of alcohol combustion rate (and, hence, resultant carbon dioxide production and oxygen consumption), tidal volume (200–1,080 ml) and respiratory frequency (8–12 min^{-1}) were adjusted to maintain end-tidal partial pressure of carbon dioxide near 40 mmHg. Before each study, the entire system was pressurized to 40 cm H_2O to check for leaks. A leak was signaled by descent of the mechanical lung or decrease in system pressure over 10 min or both. All leaks were sealed before proceeding with any experiment. A leak source was detected by the presence of bubbles, after spraying system components with soapy water.

Alcohol Combustion System to Generate CO_2 Production and O_2 Consumption

A 60-ml syringe (Becton Dickinson & Co., Franklin Lakes, NJ) installed in a precision syringe pump (Syringe pump A-99; Razel Scientific Instruments Inc., Stamford, CT) delivered an adjustable, metered flow of ethanol to a custom-made burner assembly inside the metabolic

Table 1. Precise Generation of Carbon Dioxide Production ($\dot{V}CO_2$) and Oxygen Consumption ($\dot{V}O_2$) at Six Infusion Rates of Liquid Ethanol (C_2H_5OH) into the Combustion Metabolic Chamber

Ethanol		Stoichiometry	
Q, ml/min	m, g/min	$\dot{V}O_2$, ml/min STPD	$\dot{V}CO_2$, ml/min STPD
0.043	0.034	49.9	33.3
0.087	0.068	99.9	66.6
0.173	0.137	199.7	133.1
0.260	0.205	299.6	199.7
0.347	0.274	399.4	266.3
0.433	0.342	499.3	332.8

The ethanol volumetric infusion rates for combustion in the metabolic chamber were chosen so that resultant $\dot{V}CO_2$ and $\dot{V}O_2$ would span the physiologic range of adults and children (> 12 kg body weight).

m = mass of ethanol per min; Q = volumetric infusion of ethanol; STPD = standard temperature and pressure, dry.

chamber. The alcohol was pure ethanol (100% Gold Shield Alcohol, Hayward, CA). The combustion of ethanol[15] is given by:

$$3O_2 + C_2H_5OH \rightarrow 2CO_2 + 3H_2O \quad (4)$$

so that the RQ ($\dot{V}CO_2/\dot{V}O_2$) is 2/3 (0.667).

For a given minute volume delivery (ml/min) of liquid ethanol (Q),

$$\text{Moles}_{\text{ethanol}} = \rho \cdot Q/MW\,, \quad (5)$$

where ρ is the density of ethanol (0.7893 g/cm^3) at syringe T (25°C) and MW is the molecular weight of ethanol (46.069 g/mole).

The law of Avogadro states that 1 mole of a gas has a volume of 22,414 ml STPD. Then,

$$\dot{V}CO_2\ (\text{ml/min, STPD}) = \text{Moles}_{\text{ethanol}} \cdot 2 \cdot 22{,}414\,, \quad (6)$$

and

$$\dot{V}O_2\ (\text{ml/min, STPD}) = \text{Moles}_{\text{ethanol}} \cdot 3 \cdot 22{,}414\,. \quad (7)$$

Table 1 displays the six infusion rates of alcohol into the combustion metabolic chamber and the corresponding stoichiometric generation of $\dot{V}CO_2$ and $\dot{V}O_2$. The ethanol volumetric infusion rates for combustion in the metabolic chamber were chosen so that resultant $\dot{V}CO_2$ and $\dot{V}O_2$ would span the physiologic range of adults and children (> 12 kg body weight).

Airway Humidity and Temperature Sensor

To allow conversion of airway gas flows to STPD values,[5] we have developed a fast-response humidity and temperature (T) sensor[13] (U.S. Patent No. 6,014,890, owned by Peter H. Breen, January 18, 2000), which is attached to the airway opening of the mechanical lung (fig. 2). Two tiny thermometers (copper and constantan type T thermocouples, Omega Engineering, Inc., Stamford, CT) were mounted in a standard anesthesia adapter (T adapter; Datex-Ohmeda, Milwaukee, WI). A thermocouple is formed at 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[13] (wet T). Airway gas T was measured by dry T. Humidity was measured by psychrometry,[16] 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 eight-channel back-plane; Analog Devices, Norwood, MA). The thermocouple voltage potentials were amplified approximately 5,000 times.

Data Collection

The anesthesia monitor (Capnomac Ultima) 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) (fig. 2). Oxygen fraction (F_{O_2}) and carbon dioxide fraction were measured by paramagnetic (2.0 vol% accuracy) and infrared (0.2 vol% accuracy) technologies, respectively. The Capnomac monitor routes the gas sample through water-permeable tubing (Nafion®; Dupont Fluoroproducts, Fayetteville, NC) before entering the measurement cuvettes (carbon dioxide and oxygen). 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.

Calibration of the anesthesia monitor followed the manufacturer's published procedures. Airway flow was calibrated with a 700-ml precision syringe. Gas fractions were calibrated with a precision gas mixture (5.00% CO_2, 54.5% O_2 calibration cylinder). The calibration procedure was conducted at the beginning of each experimental day, 30 min after powering up the monitor.

All signals were continuously captured (100 Hz) by an analog-to-digital acquisition PC card (DAQcard 700; National Instruments, Austin, TX) installed in a notebook computer. The digital data acquisition system was driven by a custom program (Delphi Pascal; Borland International, Scotts Valley, CA) written by our computer support specialist (David Chien, B.Sc., Department of Anesthesiology, University of California-Irvine Medical Center, Orange, California) and one author (P. H. B.).

Experimental Protocol

After initial combustion of the ethanol infusion, we waited approximately 45 min for steady state, signaled by steady values of end-tidal partial pressure of carbon dioxide (P_{ETCO_2}) and the $F_{IO_2} - F_{ETO_2}$ (end-tidal oxygen fraction) relation. Thereafter, after adjusting the rate of ethanol infusion, a new equilibrium was achieved in ap-

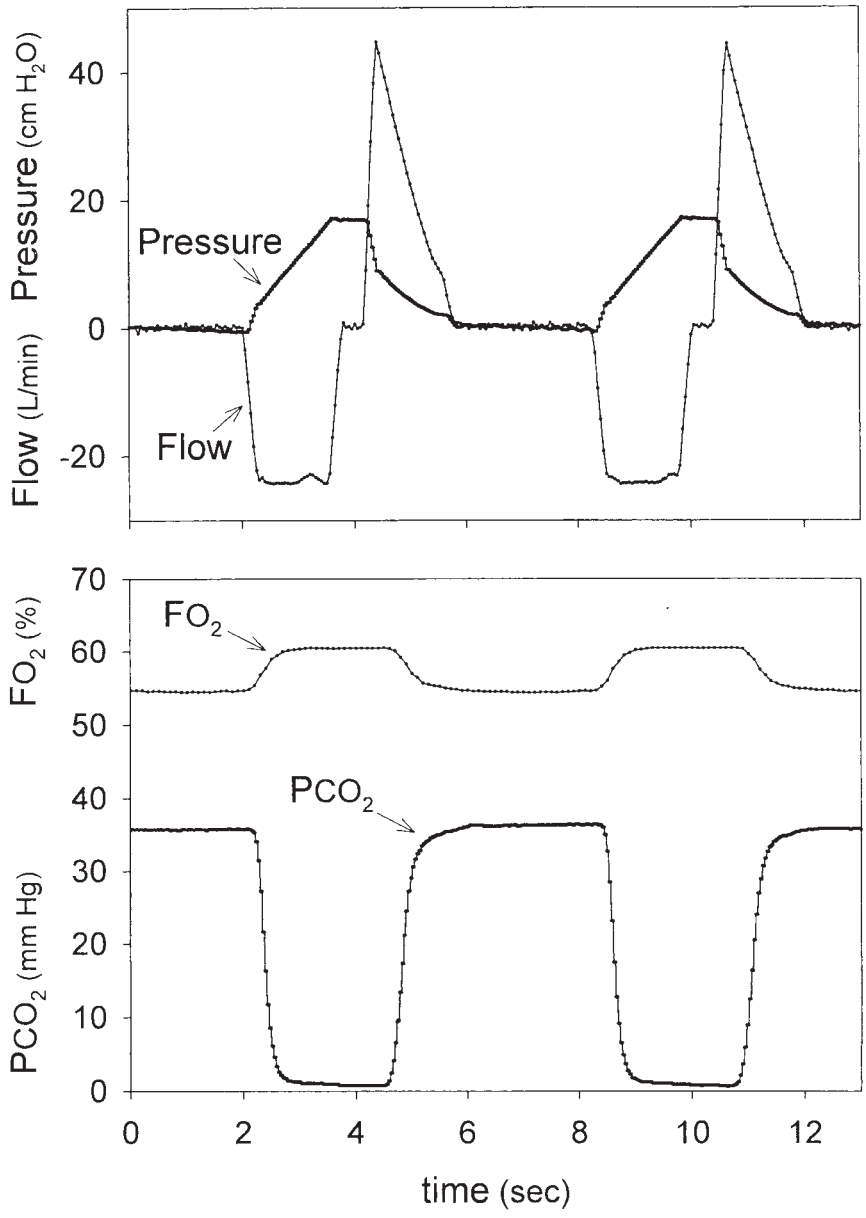

Fig. 3. Typical, actual data of two respiratory cycles. (*Top*) Airway opening pressure (*thick line*) and flow (*thin line*) *versus* time. Negative and positive flow represent inspiration and expiration, respectively. (*Bottom*) Oxygen fraction (F_{O_2}) and partial pressure of carbon dioxide (P_{CO_2}). Note the physiologic F_{O_2} waveform (normal oxygram) and P_{CO_2} waveform (normal capnogram), generated from ventilation of the respiratory dead space and the alveolar compartment of the metabolic lung simulator (fig. 2). Relative to flow, F_{O_2} and P_{CO_2} were advanced in time (1.24 and 2.84 s, respectively) to compensate for transport delay through the sidestream sampling tube. Similarly, pressure was advanced in time by 0.04 s to compensate for the measurement delay in the monitor. For graph clarity, every tenth data point was plotted for pressure, F_{O_2}, and P_{CO_2} (every fifth point for flow).

proximately 15 min. Then, the measurement sequence was conducted, consisting of the digital sampling of the following parameters for 1 min: airway flow, pressure, dry T, wet T, and bymixer $F\bar{E}_{CO_2}$, $F\bar{E}_{O_2}$, F_{ICO_2}, and F_{IO_2}. At each ethanol infusion rate, each measurement was consecutively repeated five times, 1 min apart, for the determination of reproducibility. For each experiment, this procedure was repeated at each of the six infusion rates of ethanol (table 1). The entire experiment was repeated on 4 different days.

Data Analysis

Airway $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were calculated by equations 1 and 3, respectively. Because the gas monitor does not measure nitrogen concentration directly, F_{N_2} was given by:

$$F_{N_2} = 1 - F_{CO_2} - F_{O_2}\,. \qquad (8)$$

Exhaled ventilation was calculated by:

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

where BE and EE are begin-expiration and end-expiration, respectively, of each *n*th breath, *dt* is the digital sampling period (1/100 Hz = 0.01 s), and *f* is the respiratory frequency.

Conversion to STPD conditions proceeded by:

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

where $\dot{V}$ is the airway flow measured at ambient temperature, pressure, and saturation (ATPS) conditions,

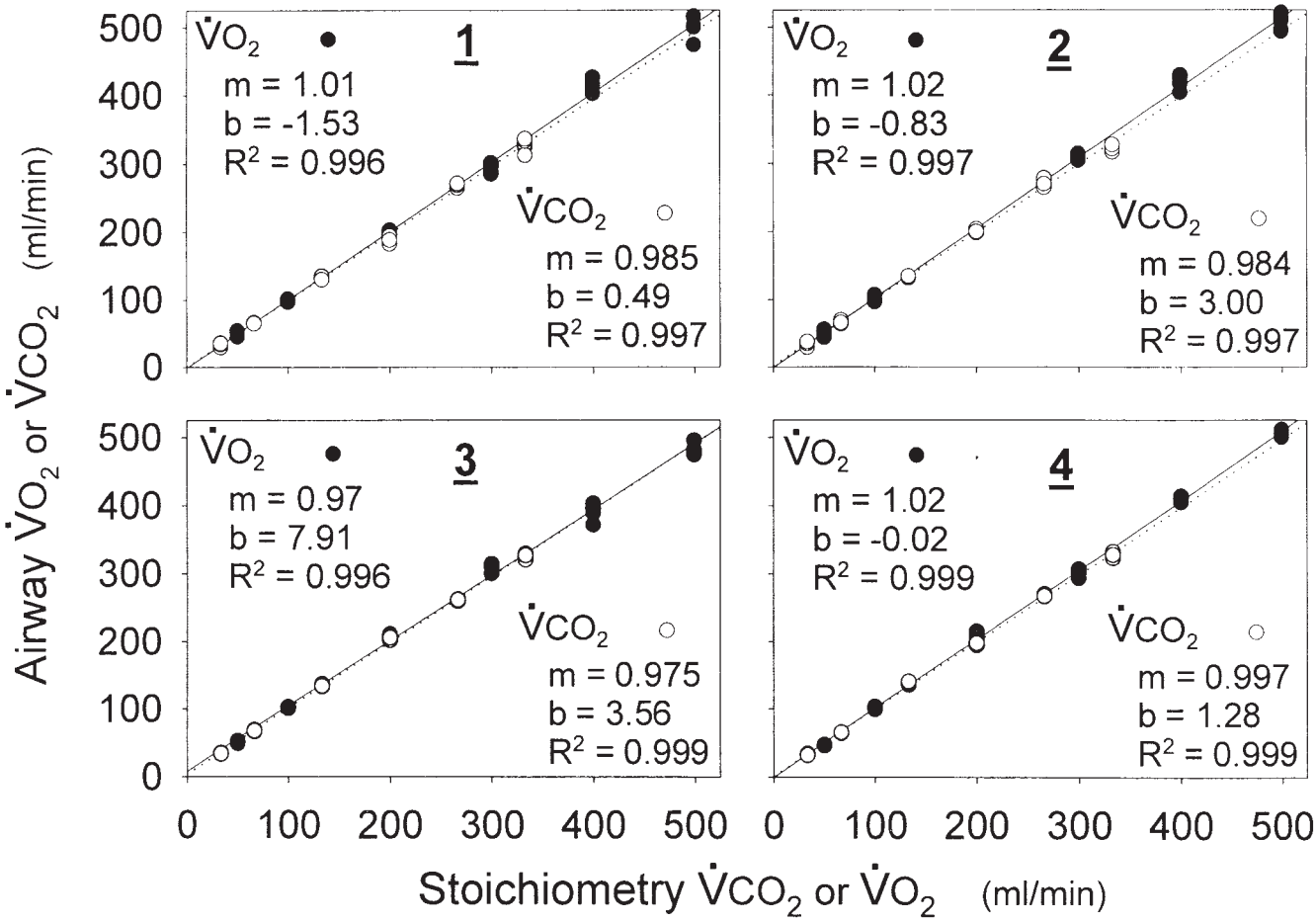

Fig. 4. Linear regression of airway measurements of carbon dioxide elimination ($\dot{V}CO_2$; *open circles* and *dotted lines*) and oxygen uptake ($\dot{V}O_2$; *solid circles* and *lines*) *versus* the stoichiometric values generated by metered ethanol combustion. Five consecutive replicate measurements are shown at each constant ethanol combustion level. Each panel was a separate experiment. b = *y* intercept; m = slope; R^2 = coefficient of determination.

PTOT is the ambient barometric pressure plus airway pressure, and P_{H_2O} is the water vapor partial pressure determined by psychrometry[16] from the airway humidity and T sensor. Equation 10 converts ATPS to STPD[5] by removing volume expansion due to water vapor (second term on right side of equation), by removing volume expansion due to thermal change above 0°C (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). If required, airway flow was processed by 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 temperature and RH and inspired and expired gas fraction measurements from the bymixers, the program automatically converted gas volumes to STPD conditions and then calculated $\dot{V}CO_2$ and $\dot{V}O_2$.

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 technique described by Bland and Altman.[17–19] Computer programs were used for data analysis (Excel spreadsheet), statistical testing (Medcalc[20]; Medcalc Software, Mariakerke, Belgium), and graphical presentation (SigmaPlot 8.0; SPSS, Chicago, IL).

Results

Figure 3 displays airway opening flow, pressure, F_{O_2}, and P_{CO_2} amid two typical respiratory cycles, during ventilation of the metabolic lung simulator. Relative to the flow signal, P_{CO_2} and F_{O_2} were shifted ahead in time by 1.24 and 2.84 s, respectively, to account for transport

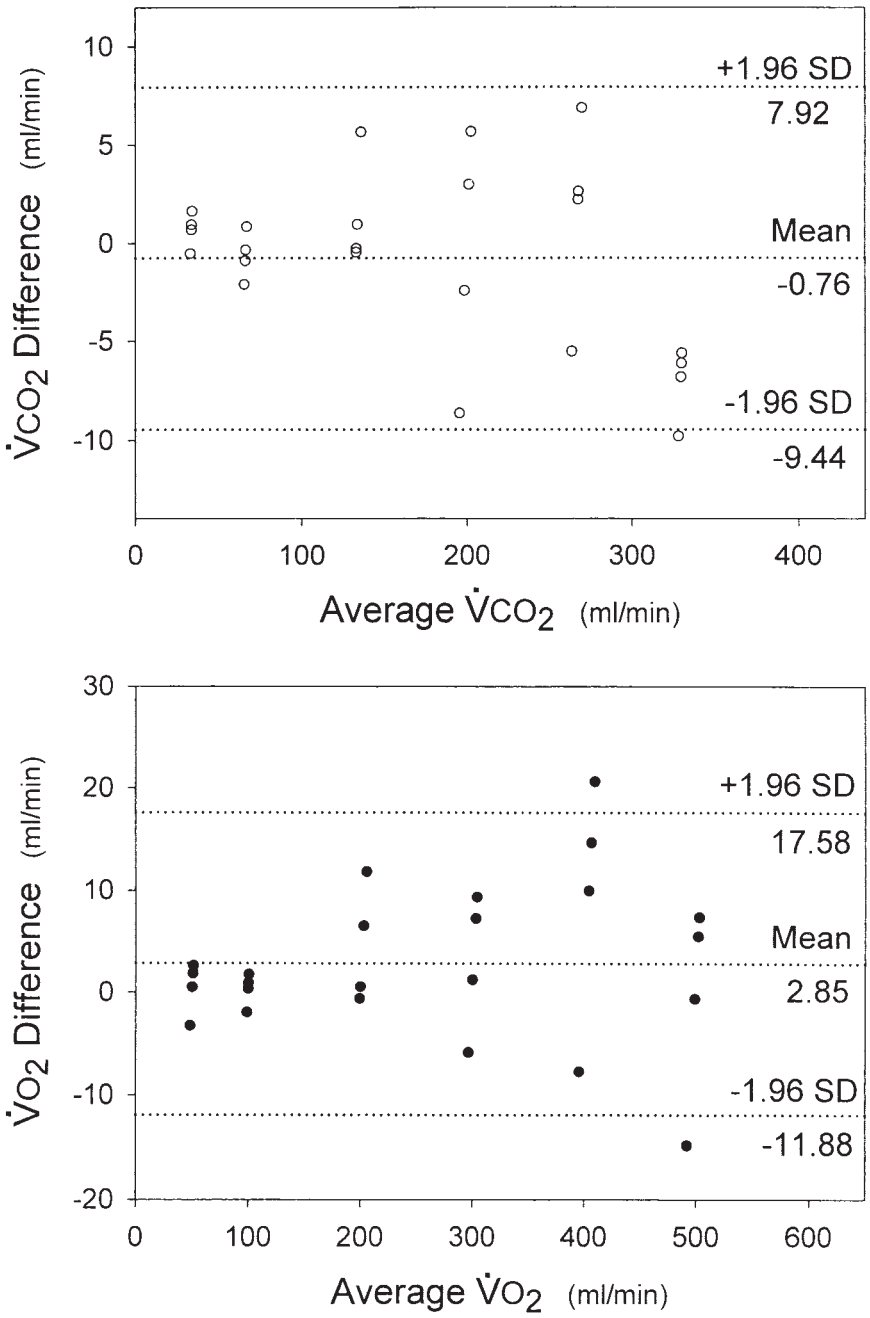

Fig. 5. Bland-Altman limits of agreement (LOA) analysis.[18,19] (*Top*) The difference between the airway measurement of $\dot{V}CO_2$ and the stoichiometric value was plotted against the average of both values. At each ethanol infusion level, $\dot{V}CO_2$ was the average of five replicate consecutive measurements. The LOA (mean ± 1.96 SD) for $\dot{V}CO_2$ were −0.8 ± 8.7 ml/min, where 95% of all points were bounded by those limits. As the average value of $\dot{V}CO_2$ increased along the *x* axis, the scatter of the differences around the mean increased along the *y* axis. Thus, greater scatter at higher values levels of $\dot{V}CO_2$ increased LOA, which then poorly reflected the accuracy of lower $\dot{V}CO_2$. (*Bottom*) The LOA for $\dot{V}O_2$ were 2.9 ± 14.7 ml/min. Similar to the *top panel*, as the average value of $\dot{V}O_2$ increased along the *x* axis, the scatter of the differences around the mean increased along the *y* axis. Again, LOA poorly reflected the smaller values of $\dot{V}O_2$.

delay during sidestream sampling. Relative to the flow signal, pressure was advanced in time by 0.04 s to account for measurement delay in the monitor. The range of inspired RH was 3–8%, and inspired temperature was 22.7–23.4°T. The range of expired RH was 39–64% (inversely proportional to minute ventilation) and expired temperature was 23.0–23.5°T. Over the range of tidal volume (200–1,080 ml), SD was nearly constant at 5.3 ml.

For each experiment, figure 4 displays the linear regression of the airway 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. Each point was the average of five consecutive replicate measurements conducted 1 min apart. When all data points were analyzed together by linear regression, for $\dot{V}CO_2$, the slope was 0.984, the y-intercept was 2.03, and R^2 was 0.999. For $\dot{V}O_2$, the slope was 1.00, the y-intercept was 1.31, and R^2 was 0.998. Therefore, the correlation between airway and stoichiometric values for both $\dot{V}CO_2$ and $\dot{V}O_2$ were excellent in all experiments.

The limits of agreement (LOA) analysis[17,19] (fig. 5) demonstrated good agreement between the airway measured values and the stoichiometric values generated by ethanol combustion. The LOA (mean ± 1.96 SD) for $\dot{V}CO_2$ were −0.76 ± 8.68 ml/min, where 95% of the points (19 of 20 trials) were bounded by those limits (fig.

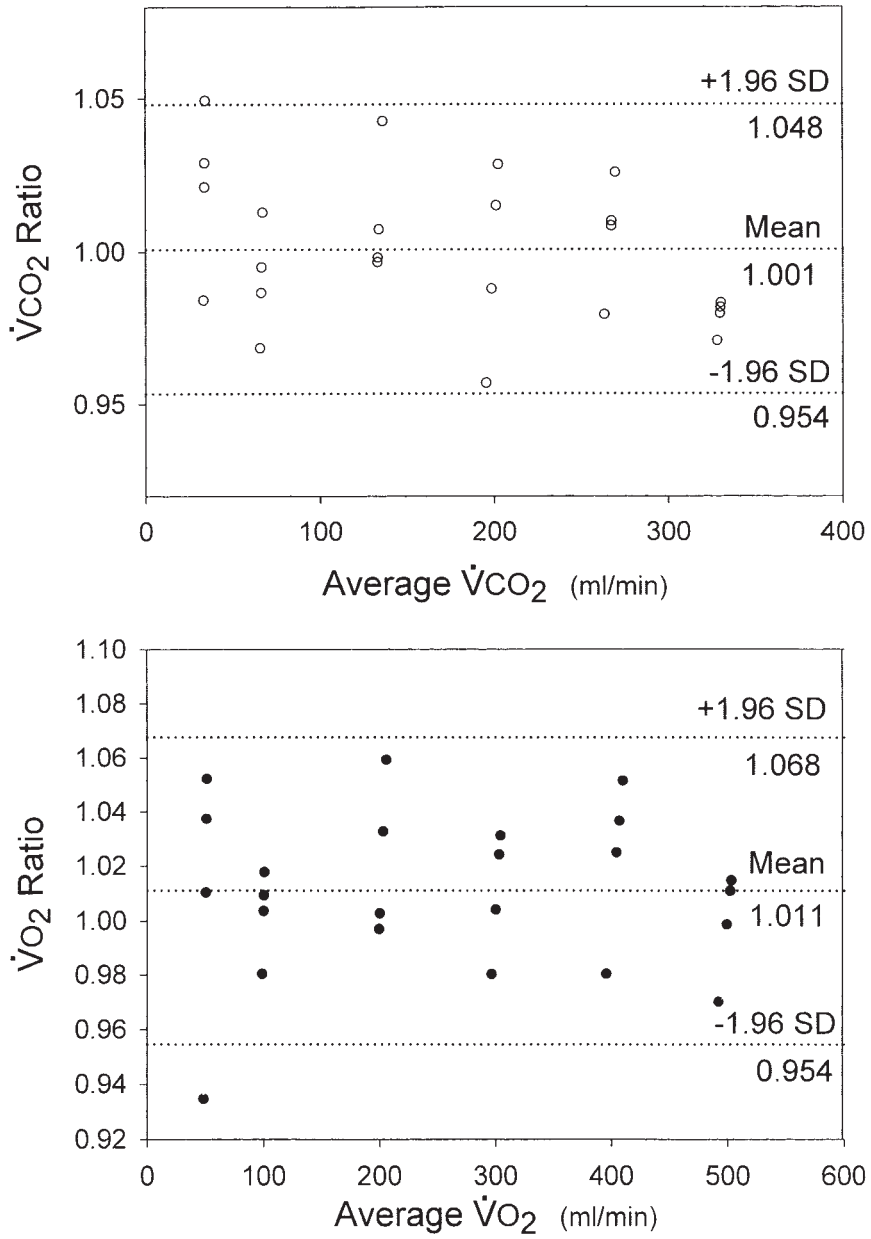

Fig. 6. Bland-Altman limits of agreement (LOA) analysis using a ratio transformation.[17,18] (*Top*) The ratio of the airway measurement of $\dot{V}CO_2$ to the stoichiometric value was plotted against the average of both values. At each ethanol infusion level, $\dot{V}CO_2$ was the average of five replicate consecutive measurements. The LOA (mean ± 1.96 SD) for $\dot{V}CO_2$ were 0.1 ± 4.7%, where 95% of all points lay within these limits. (*Bottom*) In the same analysis for $\dot{V}O_2$, the LOA were 1.1 ± 5.7%. Compared with figure 5, where LOA were calculated by plotting the difference between the airway measurement of $\dot{V}CO_2$ (or $\dot{V}O_2$) and the stoichiometric value *versus* the average of both values, the ratio plot corrected for the greater scatter of the differences at higher values of either $\dot{V}CO_2$ or $\dot{V}O_2$ and provided a better reflection of the accuracy of the data.

5, top panel, open symbols). However, as average $\dot{V}CO_2$ increased along the x-axis, the scatter of the differences around the mean increased along the y-axis. Thus, the LOA poorly reflected the accuracy of the smaller values of $\dot{V}CO_2$. In a similar analysis for $\dot{V}O_2$ (fig. 5, bottom panel, closed symbols), the LOA were 2.85 ± 14.73 ml/min. As the average value of $\dot{V}O_2$ increased along the x-axis, there was an increase in the scatter of differences around the mean along the y-axis. Again, the LOA poorly reflected the smaller values of $\dot{V}O_2$.

To account for these increases in the spread of the differences as the average value increased, the top panel of figure 6 plotted the ratio[18,20] of the airway measurement of $\dot{V}CO_2$ to the stoichiometric value *versus* the average of both values. The LOA (mean ± 1.96 SD) for $\dot{V}CO_2$ were 1.001 ± 0.047 or, expressed as a percentage, 0.1 ± 4.7%, where 95% of all points lay within these limits. In a similar analysis for $\dot{V}O_2$ (fig. 6, bottom panel), the LOA were 1.1 ± 5.7%.

The average (± SD) percent error for airway $\dot{V}CO_2$ (compared with the stoichiometric value) was 0.1 ± 2.4% (table 2). The average (± SD) percent error for airway $\dot{V}O_2$ was 1.1 ± 2.9%. The average RQ was 0.660 ± 0.013. If inspired and expired gas flows were not converted to STPD conditions, the average percent error (mean ± SD) in airway measurements of $\dot{V}CO_2$ and $\dot{V}O_2$ significantly increased (6.1 ± 5.1 and 6.8 ± 6.9%, respectively). The coefficient of variation between the consecutive measurements was 3.3% for the measurement of $\dot{V}O_2$ and 3.2% for the measurement of $\dot{V}CO_2$, which supports good reproducibility (precision) of the measurements.

Table 2. Measurements of Airway Carbon Dioxide Elimination ($\dot{V}co_2$) and Oxygen 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 Six Infusion Rates of Ethanol into the Combustion Metabolic Chamber

	$\dot{V}co_2$, ml/min			$\dot{V}o_2$, ml/min			
Experiment	Stoichiometry	Airway	% Error	Stoichiometry	Airway	% Error	RQ
1	332.8	326.7	−1.84	499.3	498.7	−0.12	0.655
	266.3	268.5	0.84	399.4	414.1	3.67	0.648
	199.7	191.1	−4.32	299.6	293.7	−1.96	0.651
	133.1	132.7	−0.35	199.7	199.1	−0.30	0.666
	66.6	65.7	−1.35	99.9	97.9	−1.95	0.671
	33.3	34.2	2.88	49.9	51.8	3.75	0.661
2	332.8	323.1	−2.94	499.3	506.7	1.48	0.638
	266.3	273.1	2.58	399.4	420.0	5.17	0.650
	199.7	202.7	1.50	299.6	306.8	2.43	0.661
	133.1	132.9	−0.20	199.7	200.3	0.28	0.663
	66.6	66.2	−0.51	99.9	100.2	0.37	0.661
	33.3	34.9	4.93	49.9	52.5	5.23	0.665
3	332.8	326.0	−2.04	499.3	484.5	−2.97	0.673
	266.3	260.8	−2.07	399.4	391.7	−1.94	0.666
	199.7	205.4	2.84	299.6	308.9	3.13	0.665
	133.1	134.1	0.73	199.7	206.2	3.27	0.650
	66.6	67.4	1.25	99.9	101.6	1.78	0.663
	33.3	34.0	2.10	49.9	50.5	1.04	0.674
4	332.8	327.2	−1.68	499.3	504.8	1.11	0.648
	266.3	268.9	1.00	399.4	409.4	2.50	0.657
	199.7	197.3	−1.22	299.6	300.8	0.42	0.656
	133.1	138.8	4.24	199.7	211.5	5.93	0.656
	66.6	64.5	−3.17	99.9	100.8	0.94	0.640
	33.3	32.8	−1.59	49.9	46.7	−6.53	0.702
Mean			0.07			1.11	0.660
± SD			2.41			2.88	± 0.013
± 1.96 SD			4.73			5.65	

Four experiments, on separate days, are shown. Each value was the average of five consecutive replicate measurements. For $\dot{V}co_2$ and $\dot{V}o_2$, % error = 100 · (airway − stoichiometry)/stoichiometry.

RQ = respiratory quotient ($\dot{V}co_2/\dot{V}o_2$); SD = standard deviation.

Discussion

This study demonstrates for the first time that the bymixer can measure mixed expired gas fractions in an open ventilatory circuit to generate, along with a measurement of exhaled ventilation, accurate determinations of airway $\dot{V}co_2$ and $\dot{V}o_2$. Compared with the reference standard values in the metabolic lung simulator (combustion of metered ethanol), the average (± SD) percent error of $\dot{V}co_2$ was 0.1 ± 2.4%, and the percent error of $\dot{V}o_2$ was 1.1 ± 2.9%. Inspection of the linear regression analysis (fig. 4) demonstrates excellent correlation of airway $\dot{V}co_2$ and $\dot{V}o_2$ *versus* the stoichiometric values. Similarly, the LOA analysis put forth by Bland-Altman[17,19] (figs. 5 and 6) demonstrated excellent agreement between the airway and stoichiometric values (especially when the ratios plot, fig. 6, accounted for the increase in differences as the average value of $\dot{V}co_2$ or $\dot{V}o_2$ increased) and is considered acceptable for clinical measurements.

In particular, note the precise determinations of the respiratory quotient, RQ (0.660 ± 0.013). RQ is a sensitive parameter because it is the ratio of two airway measurements ($\dot{V}co_2/\dot{V}o_2$). This high precision of measured airway RQ presents a reliable indicator for metabolic monitoring and clinical decisions.[2]

The LOA for $\dot{V}co_2$ (difference between airway and stoichiometric value *vs.* the mean value) were −0.76 ± 8.68 ml/min (fig. 5, top panel), which encompasses 95% of the points. However, as $\dot{V}co_2$ increased along the x-axis to its maximum value of approximately 300 ml/min, the difference between the airway and stoichiometric measurements progressively increased. Thus, the high values of $\dot{V}co_2$ increased the LOA, generating limits that poorly represented the accuracy of smaller values of $\dot{V}co_2$. For example, for a given $\dot{V}co_2$ of 300 ml/min, the LOA place the maximum error at 9.4 ml/min below the real value (290.6 ml/min), which is a percent error of 3.1%, within the expected error range (table 2; mean ± 1.96 SD). However, for a given $\dot{V}co_2$ of 33.3 ml/min, the LOA place the maximum error for the measurement at 9.4 ml/min below the real value (23.9 ml/min), which is an error of 28.3%, far in excess of the expected error range.

Accordingly, to provide a more accurate reflection of the difference between the airway and stoichiometric measurements, the data were plotted as a ratio of the

two values *versus* the mean value (fig. 6, top panel). The LOA for the ratio plot were 0.1 ± 4.7%. Although the error limit for the larger values of $\dot{V}_{CO_2}$ increased slightly from 3.1 to 4.8%, the limit for the lesser values decreased significantly from 28.3% to 4.8%. These limits for $\dot{V}_{CO_2}$ compare well with the expected error range (table 2; mean ± 1.96 SD) and support the overall accuracy of the measurement.

A similar analysis was performed for $\dot{V}_{O_2}$. For the plot of the difference of the airway and stoichiometric value *versus* the mean of the two values (fig. 5, bottom panel), the LOA were 2.9 ± 14.7 ml/min. Inspection of the graph reveals that, as the values of $\dot{V}_{O_2}$ increased along the x-axis, the differences between the airway and stoichiometric measurements increased, which was also evident in the linear regression analysis (fig. 4, solid symbols). Thus, the LOA were increased by high values of $\dot{V}_{O_2}$, with poor reflection of the accuracy of low values of $\dot{V}_{O_2}$. For example, for a given $\dot{V}_{O_2}$ of 49.9 ml/min, the LOA place the maximum error at 17.6 ml/min above the actual value (error of 35.2%), well in excess of the expected error range (table 2). To better represent the data, the plot of the airway/stoichiometric measurement ratio *versus* the average value of $\dot{V}_{O_2}$ (fig. 6, bottom panel) generated LOA of 1.1 ± 5.7%, for a maximum error of 6.8%, similar to the expected error range (table 2; mean ± 1.96 SD).

Although the above LOA analysis is the most accepted method to assess the accuracy of the bymixer-flow airway measurements of indirect calorimetry, additional information can be gleaned by inspection of the individual linear regression plots for each experiment (fig. 4). Undetected, tiny leaks in the metabolic lung simulator can cause small systematic effects on the slope and y-intercept of the plots of airway measurements *versus* the stoichiometric values of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ generated by the metered combustion of ethanol.

To explore the repeatability or precision of the measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, at a given ethanol combustion level, we examined how five consecutive, replicate measurements agreed with one another. The raw data revealed that the variability of the measurements increased at higher values of $\dot{V}_{CO_2}$ or $\dot{V}_{O_2}$. To account for this phenomenon, the coefficient of variation (SD divided by the mean) was used to quantify the precision of the measurement. For the measurement of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, the coefficient of variations were 3.2 and 3.3%, respectively, supporting good precision of the measurements.

We chose to perform this study using a F_{IO_2} of 60% (F_{IN_2} [inspired nitrogen fraction] = 40%) because most patients in the critical care environment are ventilated with oxygen fractions at or below this level. The accuracy of our bymixer-airway flow measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ should even be better at lower F_{IO_2} because the fraction of nitrogen increases in the respiratory gas (equation 3). Similar to commercial monitors, our indirect calorimetry system does not directly measure F_{N_2} (nitrogen fraction). Instead, F_{N_2} is calculated by subtracting the other gas fractions from unity (equation 8). If available, a mass spectrometer[21] can directly measure F_{N_2} and potentially improve accuracy of the measurements of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$.

Conservation of the inert gas nitrogen (Haldane transformation) allows determination of the volume difference between inspiration and expiration due to differences in inspired and expired T and humidity.[5] Classic respiratory physiology emphasizes that steady state (including stable inspired gas concentration and lung end-expired volume) is mandatory for the nitrogen conservation principle.[22] Values of ventilation, gas circulation between the metabolic chamber and the mechanical lung, and ethanol combustion in the metabolic chamber must also be in steady state to allow comparisons of indirect calorimetry *versus* values of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ generated by the metabolic chamber. We took care in the experiments to ensure equilibrium before conducting the measurement sequences. A limitation of the Haldane transformation in the anesthesia environment is the inability to use inspired nitrous oxide. The Haldane transformation is defined for nitrogen, an insoluble inert gas, where nitrogen balance during steady state can be harnessed to express inspired volume in terms of nitrogen fractions and expired volume (equations 2 and 3). For these purposes, nitrous oxide is too soluble in the body, rarely reaches true equilibrium, and cannot be used in the Haldane transformation.

In this study, the bymixer mixing chamber volume (fig. 1) was set to 200 ml, which generated a bymixer response of approximately 90 s.[9] For faster response, the mixing chamber volume could be decreased to 100 ml, which would allow bymixer measurements to update every 30 s. The adjustment of mixing chamber volume can proceed during actual clinical ventilation without disconnection of any circuit component. The bymixer added only negligible resistance to gas flow because the internal diameter of the main flow channel was similar to standard ventilation circuit tubes.[9] The resistor in the bypass flow tube resulted in a bypass:total flow ratio of approximately 1:9. However, because of the behavior of parallel resistors ($1/R_{BYMIXER} = 1/R_{MAIN} + 1/R_{BYPASS}$), the bypass flow actually slightly reduced the total resistance of the bymixer below the value of the main flow channel.

The metabolic lung simulator added warmth and water vapor to exhaled airway gas flow. If gas flow was not corrected to the STPD condition, the error of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, compared with the reference standard of alcohol combustion, significantly increased. That ventilated patients have higher exhaled gas temperature and RH (compared to the metabolic lung simulator) makes the correction of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to STPD conditions even more important. We have developed a fast-response air-

way sensor of humidity and temperature,[13] suitable for the clinical ventilation, which provided continuous airway opening measurements of T and RH to allow STPD correction of gas flow.

Development of an accurate and stable metabolic lung simulator required considerable effort. This bench apparatus was an absolute requirement to perform the validation of the bymixer-airway flow measurements of $\dot{V}CO_2$, $\dot{V}O_2$, and RQ for several reasons. First, there are no available, accurate reference standard measurements of $\dot{V}CO_2$ and $\dot{V}O_2$ in critical care medicine or during anesthesia care. Second, in patients, it is difficult to both maintain and confirm presence of steady state, which is mandatory for validation data collections. Third, the metabolic lung simulator can quickly and accurately generate a wide range of $\dot{V}CO_2$ and $\dot{V}O_2$, which would be impossible in patient studies. The mechanical lung closely simulates the resistance, compliance, and dead space characteristics of the human respiratory system. Figure 3 depicts normal airway opening flow and pressure waveforms (top panel) during mechanical ventilation of the metabolic lung simulator, generating a physiologic oxygram and capnogram. Presence of anatomical dead space was mandatory; otherwise, the alveolar gas fractions would have been similar to the values in the expired limb of the ventilation circuit.

In conclusion, the new clinical bymixer allows measurements of indirect calorimetry ($\dot{V}CO_2$, $\dot{V}O_2$, and RQ) whenever basic expired flow and gas monitoring measurements are in use for the patient, without the need for expensive, dedicated, and complex equipment. In contrast to the gas collection bag or metabolic monitor, the bymixer can also measure gas fractions in the inspired limb of the ventilation circuit, for conditions in which inspired gas fractions are not stable. Also, the bymixer offers the first opportunity, we believe, to measure mixed gas concentrations in the inspired and expired limb of the common anesthesia circle ventilation circuit, which will be the subject of a future investigation. The accuracy of the bymixer-airway flow measurements of indirect calorimetry compare favorably with the accuracy of commercial monitors.[3,7,23]

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