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ORIGINAL RESEARCH

Evaluation and application of a method for estimating nasal end-tidal O_2 fraction while administering supplemental O_2

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Abstract

This paper describes a method for estimating the oxygen enhanced end-tidal fraction of oxygen ($F_{ET}O_e$), the end-tidal fraction of oxygen ($F_{ET}O_2$) that is raised by administering supplemental oxygen. The paper has two purposes: the first is to evaluate the method's accuracy on the bench and in volunteers; the second purpose is to demonstrate how to apply the method to compare two techniques of oxygen administration. The method estimates $F_{ET}O_e$ by analyzing expired oxygen as oxygen washes out of the lung. The method for estimating $F_{ET}O_e$ was first validated using a bench simulation in which tracheal oxygen was measured directly. Then it was evaluated in 30 healthy volunteers and compared to the bench simulation. Bland–Altman analysis compared calculated and observed $F_{ET}O_e/F_{ET}O_2$ measurements. After the method was evaluated, it was implemented to compare the $F_{ET}O_e$ obtained when administering oxygen using two different techniques (pulsed and continuous flow). A total of eighteen breath washout conditions were evaluated on the bench. $F_{ET}O_e$ estimates and tracheal $F_{ET}O_2$ had a mean difference of -0.016 FO_2 with 95% limits of agreement from -0.048 to 0.016 FO_2. Thirteen breath washouts per volunteer were analyzed. Extrapolated and observed $F_{ET}O_2$ had a mean difference of -0.001 FO_2 with 95% limits of agreement from -0.006 to 0.004 FO_2. Pulsed flow oxygen (PFO) achieved the same $F_{ET}O_e$ values as continuous flow oxygen (CFO) using 32.1% ± 2.27% (mean ± SD) of the CFO rate. This paper has demonstrated that the method estimates $F_{ET}O_2$ enhanced by administering supplemental oxygen with clinically insignificant differences. This paper has also shown that PFO can obtain $F_{ET}O_2$ similar to CFO using approximately one-third of the oxygen volume. After evaluating this method, we conclude that the method provides useful estimates of nasal $F_{ET}O_2$ enhanced by supplemental oxygen administration.

Keywords Nasal end-tidal O_2 fraction measurement · Mathematical modeling · Pulsed flow oxygen · Continuous flow oxygen

1 Introduction

Oxygraphy can help assess pulmonary oxygen reserve during preoxygenation by graphically displaying inhaled and exhaled fraction of oxygen (FO_2) [1]. When preoxygenating before inducing general anesthesia, the oxygram shows the end-tidal O_2 fraction ($F_{ET}O_2$) increase from 0.16 to ~0.96. Edmark et al. [2] have shown if a patient is not completely preoxygenated before induction, their oxygen saturation (SpO_2) drops to 90% significantly faster during a subsequent apnea. For example, SpO_2 dropped to 90% over 3 min faster in patients with a $F_{ET}O_2$ of only 0.53 prior to apnea than in patients with a $F_{ET}O_2$ of 0.93 [2]. These findings show how important measuring $F_{ET}O_2$ prior to induction is, especially when expecting difficult intubation, apneic periods, or when a patient has cardiorespiratory impairment [1].

Although pulse oximetry and capnography are used more commonly, oxygraphy with $F_{ET}O_2$ also serves as a useful surrogate of ventilation [1, 3]. During general anesthesia, a low $F_{ET}O_2$ can indicate inadequate ventilation, reveal hypoxic gas mixtures, detect imminent hypoxemia earlier than pulse oximetry, and detect hypoventilation earlier than capnography [1, 4–6].

Although accurate for sampling from the breathing circuit during general anesthesia, sampling oxygraphy via nasal cannula in non-intubated patients is much less accurate because supplemental oxygen mixes with the exhaled gas, artificially elevating the end-tidal sample. Therefore, in non-intubated patients, measuring $F_{ET}O_2$

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can only achieve acceptable accuracy when supplemental oxygen flow is off. This constraint prevents nasal oxygraphy from assessing supra-ambient levels of oxygen such as oxygen reserve. Also, supplemental oxygen prevents nasal oxygraphy from monitoring ventilation. Given that supplemental oxygen compromises pulse oximetry's ability to detect inadequate respiration [7–9] and dilutes nasal end-tidal carbon dioxide [10–13], monitoring respiration is challenging while administering supplemental oxygen.

The $F_{ET}O_2$ enhanced by administering supplemental oxygen, which is referred to here as $F_{ET}O_e$, is the supra-ambient $F_{ET}O_2$ that oxygraphy would measure if oxygen delivery did not contaminate nasal end-tidal gas (Fig. 1). The method detailed below estimates $F_{ET}O_e$ by collecting $F_{ET}O_2$ while discontinuing supplemental oxygen briefly and then analyzing $F_{ET}O_2$ to determine a model coefficient. This method may be able to estimate $F_{ET}O_e$ with clinically insignificant differences (limits of agreement (LOA) within ± 0.05 FO_2).

This paper has two purposes. The first is to describe how the method estimates $F_{ET}O_e$ and to evaluate it on the bench and in volunteers. The second purpose is to demonstrate one example of how to apply the method to compare two techniques of oxygen administration (pulsed and continuous flow).

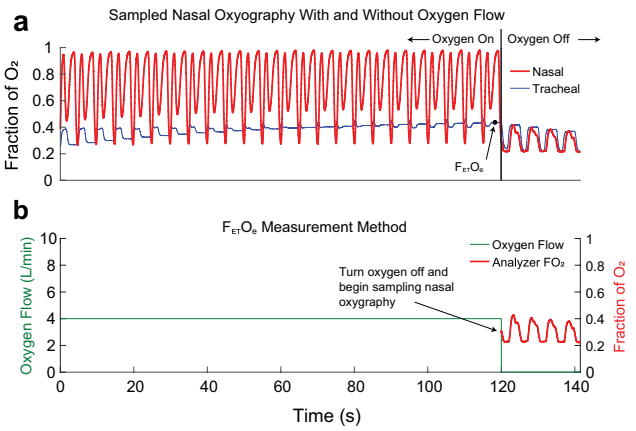

Fig. 1 Visual portrayal of **a** nasal oxygram with and without oxygen flow and of **b** the method for estimating supplemental oxygen enhanced end-tidal O_2 fraction ($F_{ET}O_e$). **a** While administering oxygen, nasal fraction of O_2 fluctuates from 0.25 to 0.95 while the tracheal oxygram shows that $F_{ET}O_e$ is slowly increasing. After oxygen flow is turned off, nasal and tracheal $F_{ET}O_2$ are the same. **b** The method detailed in this paper may be able to estimate $F_{ET}O_e$ by using an automated system to temporarily turn off oxygen flow. After turning off oxygen flow, the method analyzes changes in $F_{ET}O_2$ as oxygen washes out to estimate $F_{ET}O_e$

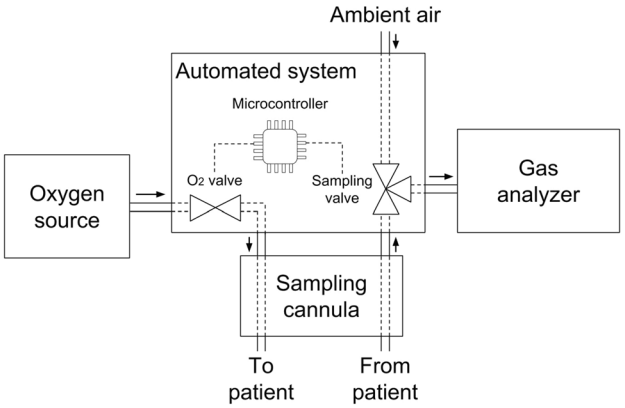

Fig. 2 Schematic diagram of the oxygen sampling system

2 Methods

2.1 Method for estimating nasal end-tidal O_2 fraction

The method for estimating $F_{ET}O_e$ uses a breath-by-breath model to estimate $F_{ET}O_e$ and an automated system to control oxygen flow and nasal gas sampling. To estimate $F_{ET}O_e$, the method analyzes each breath's $F_{ET}O_2$ from the oxygram as oxygen washes out from the lung. The method can measure $F_{ET}O_2$ accurately since during this time the oxygen flow is off.

2.1.1 Description of the method

Nasal FO_2 cannot be measured when administering continuous flow oxygen (CFO). Figure 1a shows how administering oxygen distorts the oxygram throughout the breath cycle. Administering oxygen alters FO_2 when expiratory and inspiratory flows are lower than the oxygen delivery rate such as during end-expiratory pause and late inspiration. Because administering supplemental oxygen distorts the oxygram, measuring $F_{ET}O_e$ is challenging while administering oxygen via nasal cannula.

Although $F_{ET}O_e$ cannot be measured directly, it may be possible to estimate it using an automated system and extrapolation (Fig. 1b). The method detailed in this paper estimates $F_{ET}O_e$ by using an automated system to turn off oxygen flow temporarily. By turning off oxygen flow, the automated system facilitates accurate measurement of $F_{ET}O_2$. Turning oxygen off lowers the fraction of inspired oxygen (FiO_2) to 0.21, and spontaneous breathing washes oxygen out of the lung. As oxygen washes out of the lung, the $F_{ET}O_e$ estimation method analyzes changes in $F_{ET}O_2$ with each of the four breaths to extrapolate $F_{ET}O_e$.

2.1.2 Automated oxygen sampling system

The automated system interfaces with a sampling nasal cannula (Fig. 2). A two-way oxygen valve (MD PRO, Parker Hannifin, Hollis, NH) controls oxygen flow from a compressed oxygen source to the patient. A three-way sampling valve (LFAA0509415H, The Lee Co, Essex, CT) enables and disables nasal gas sampling. During oxygen delivery the oxygen valve is open, and the sampling valve is off. Before estimating $F_{ET}O_e$, the system shuts off oxygen flow and enables nasal sampling. After collecting $F_{ET}O_2$ values from the breath washout sequence, the system opens the oxygen valve and disables nasal gas sampling.

2.1.3 Theoretical aspects

While discontinuing oxygen flow, the method collects four breath-by-breath $F_{ET}O_2$ measurements as oxygen washes out of the lung. The breath-by-breath model that estimates $F_{ET}O_e$ is composed of two volumes: effective functional residual capacity (FRC) volume and alveolar tidal volume (Vt). The model estimates $F_{ET}O_e$ using the breath-by-breath mixing of these two volumes and extrapolating backward in time.

Before an oxygen washout, the $F_{ET}O_e$ is approximately the same as the alveolar oxygen fraction [14]. During each breath of an oxygen washout, Vt decreases $F_{ET}O_2$ by a factor until $F_{ET}O_2$ reaches the $F_{ET}O_2$ when breathing room air (FEO_{air}). The ratio Vt/(Vt + FRC) determines the factor and $F_{ET}O_2$ decreases exponentially since each $F_{ET}O_2$ is a fraction of the previous breath's $F_{ET}O_2$.

The method for estimating $F_{ET}O_e$ analyzes $F_{ET}O_2$ from the first three washout breaths to determine the factor by which $F_{ET}O_2$ is declining. This factor determines the breath-by-breath model coefficient, α, which best represents the $F_{ET}O_2$ washout. After calculating this coefficient, the method uses the washout-specific model to extrapolate backward and estimate $F_{ET}O_e$.

A first-order difference equation is used for estimating $F_{ET}O_e$:

$$F_{ET}O_2[b] = (1-\alpha)\cdot F_{ET}O_2[b-1] + \alpha \cdot F_{ET}O_{air}, \quad (1)$$

where b is the number of the current breath, $F_{ET}O_2[b]$ is the $F_{ET}O_2$ to be modeled, $F_{ET}O_2[b-1]$ is the $F_{ET}O_2$ from the previous breath, $F_{ET}O_{air}$ is the $F_{ET}O_2$ when FiO_2 is 0.21, and α is the model coefficient.

2.1.4 Determining the model coefficient

The model coefficient characterizes at what rate $F_{ET}O_2$ approaches $F_{ET}O_{air}$. Since the coefficient can vary from washout to washout, the $F_{ET}O_e$ method must determine a washout-specific coefficient. By rearranging Eq. 1 and substituting for alpha, the method can calculate the model coefficient that best fits $F_{ET}O_2$ values from the washout:

$$\frac{Vt}{Vt+FRC} = \alpha = \frac{F_{ET}O_2[b] - F_{ET}O_2[b+1]}{F_{ET}O_2[b] - F_{ET}O_{air}}. \quad (2)$$

Note that α only depends on the ratio Vt/(Vt + FRC). Since the method for estimating $F_{ET}O_e$ does not measure Vt of FRC directly, α only represents the portion of the FRC and tidal volume that mix with each other. These portions are the effective FRC and alveolar Vt.

2.1.5 Estimating the supplemental oxygen enhanced $F_{ET}O_2$

If Vt during the breath washout stays fairly consistent, all breaths of the washout will have the same α coefficient, and the model can use the $F_{ET}O_2$ from Breath 1 to estimate $F_{ET}O_e$. After using Eq. 2 to determine the coefficient specific to a washout, the method uses that coefficient (Eq. 1) to estimate $F_{ET}O_e$. Solving Eq. 1 for $F_{ET}O_2[b-1]$ gives the equation for calculating the previous breath's $F_{ET}O_2$:

$$F_{ET}O_2[b-1] = \frac{F_{ET}O_2[b] - \alpha \cdot F_{ET}O_{air}}{1-\alpha}. \quad (3)$$

Equation 3 is useful for determining $F_{ET}O_e$ because it can extrapolate backward to calculate the previous $F_{ET}O_2$. When using Eq. 3 to estimate $F_{ET}O_e$, the method uses the first breath (Breath 1) of the washout as $F_{ET}O_2[b]$ (Fig. 3).

2.2 Test setup and protocol

2.2.1 Bench validation

Figure 4 shows the setup for the bench validation. To simulate spontaneous breathing, a ventilator (Respironics V60, Philips, Carlsbad, CA) ventilated one side of a lung model (Training Test Lung, Michigan Instruments, Kentwood, MI) which was coupled to the second chamber of the test lung [15, 16]. A fan inside the lung ensured oxygen was distributed evenly. Test lung compliance was 0.05 L/cm H_2O, and a 5.6 mm orifice resistor simulated airway resistance (Michigan Instruments, Kentwood, MI).

Testing used an upper airway replica (Nose-Throat Geometry, Respiratory Drug Delivery, Richmond, VA) [17]. A nasal cannula (Softech Bi-Flo, Teleflex, Morrisville, NC) was connected to the oxygen sampling system and placed into the nares. The trachea was attached to the spontaneous breathing chamber of the test lung using enough corrugated tubing to create 150 mL of dead space. The sampling line of the nasal cannula was connected to a gas analyzer (CapnoMAC, Datex, Helsinki, Finland) to measure the nasal oxygram. The analyzer's response time

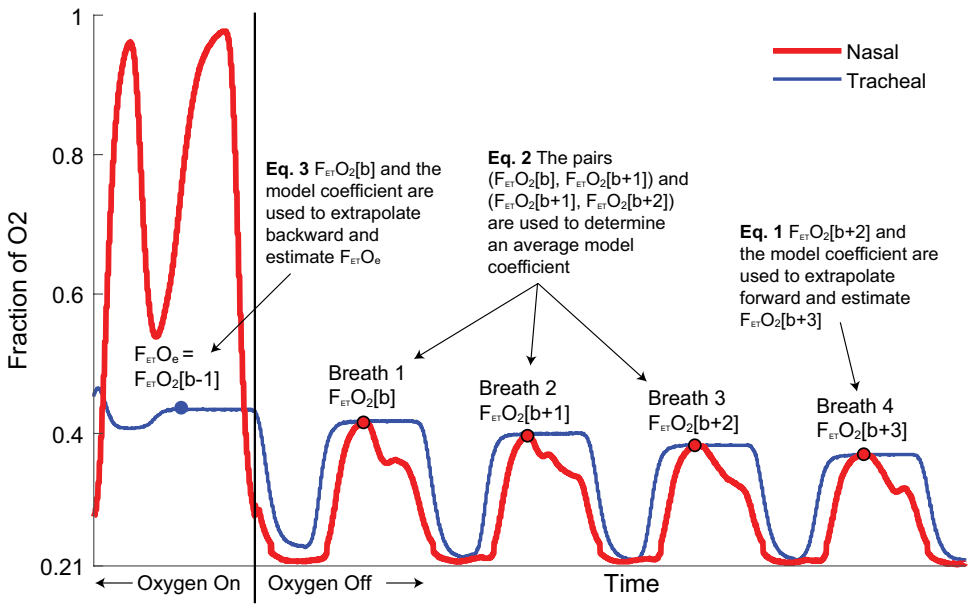

Fig. 3 Visual portrayal of how the method calculates $F_{ET}O_e$ on the bench. For the bench setup, $F_{ET}O_{air}$ is 0.21 since the fraction of inspired oxygen was 0.21 when breathing room air and the test lung did not consume any oxygen. During the volunteer study, $F_{ET}O_{air}$ was measured for each volunteer at the beginning of the study

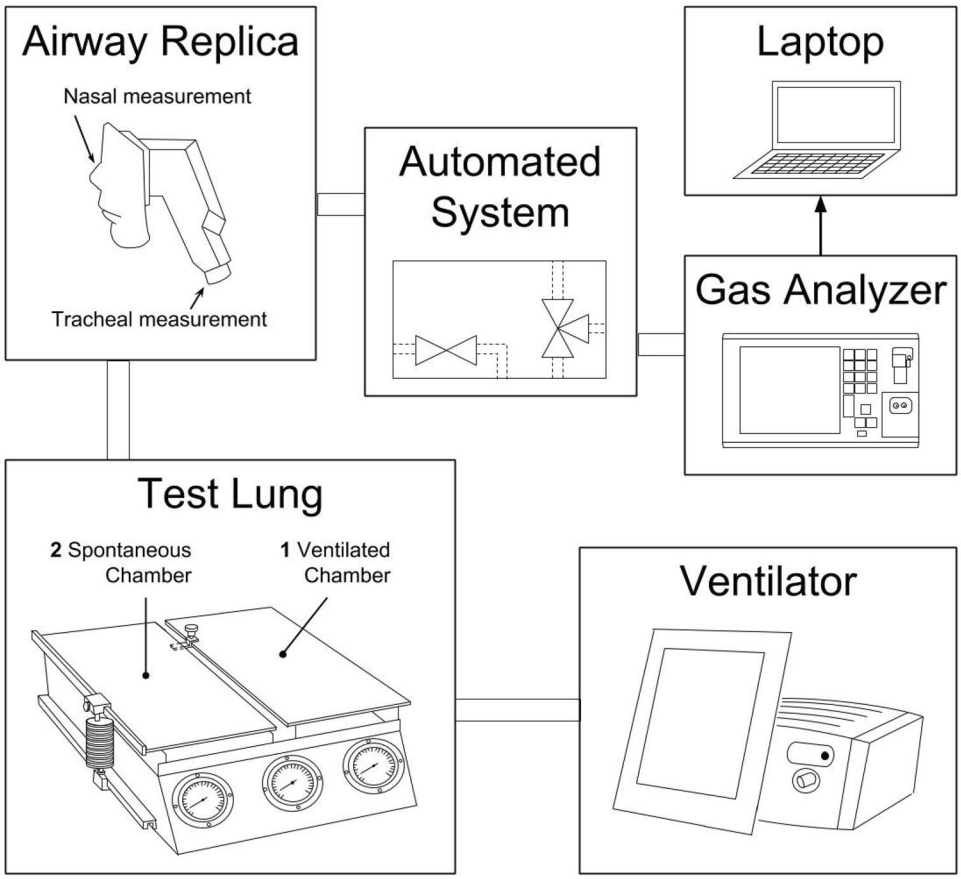

Fig. 4 Experimental setup for the bench validation

(< 500 ms) was short enough to measure $F_{ET}O_2$. A separate gas sampling line (ZML-9530-1, Salter Labs, Carlsbad, CA) measured the tracheal oxygram, which was used to validate the method for estimating $F_{ET}O_e$.

The estimation method was validated at a wide range of $F_{ET}O_2$ values (0.25–0.90) with the ventilator set to a Vt of 300 or 500 mL and a respiratory rate of 12 breaths per minute. Each breath washout was collected after a two-minute

period of oxygen delivery and with oxygen flow off for four breaths. After sampling oxygen concentration for four breaths, the system began administering the next flow rate.

The gas analyzer sampled $F_{ET}O_2$ from the nasal cannula during the four breath washout. Breaths 1 to 3 were used to calculate the α coefficient of the washout-specific model. The washout-specific model and the $F_{ET}O_2$ from Breath 1 then extrapolated $F_{ET}O_e$ (Fig. 3). Also, the model and the $F_{ET}O_2$ from Breath 1 simulated $F_{ET}O_2$ for Breaths 2–4.

For the remainder of this manuscript, since Breath 2 and 3 $F_{ET}O_2$ is used to calculate the model's α coefficient, we will refer to estimating their $F_{ET}O_2$ as interpolation. Since $F_{ET}O_e$ and Breath 4 $F_{ET}O_2$ are not used to calculate α, we will refer to estimating them as backward and forward extrapolation, respectively (see Fig. 3).

2.2.2 Volunteer evaluation

The method was evaluated in 30 healthy volunteers. Volunteers were fitted with a nasal cannula connected to the automated system. The main difference between the bench and volunteer studies was that the volunteer study did not sample tracheal oxygraphy. Instead, simulation performance was compared between the bench and volunteers for interpolation and forward extrapolation. If LOA on the bench and in volunteers were clinically insignificant, then backward extrapolation of $F_{ET}O_e$ in volunteers would also be clinically insignificant.

The gas analyzer did not sample gas while administering oxygen to avoid affecting oxygen delivery [18, 19]. Since $F_{ET}O_{air}$ varies between volunteers, it was measured for each volunteer at the beginning of the study before administering any oxygen. Estimated FRC was calculated using Quanjer's equation to determine the study volunteers' ranges of estimated FRC [20].

Bland–Altman analysis was used to evaluate the method's simulations of $F_{ET}O_2$ [21]. Mean differences and 95% LOA between inter/extrapolated values and observed measurements were calculated using the R software package *BlandAltmanLeh* (Version 0.3.1, Lehnert, 2015). Note that because the method used the $F_{ET}O_2$ of Breath 1 as an input, the performance of that breath was not evaluated.

2.3 Comparing pulsed and continuous flow oxygen

The method was implemented to compare two techniques for administering oxygen: continuous flow oxygen (CFO) and pulsed flow oxygen (PFO). Both of these therapies administer oxygen during inhalation while only CFO administers oxygen during exhalation. Although less common, PFO administers oxygen more efficiently because it administers oxygen only during early inhalation when most of the oxygen will reach the alveoli.

Comparing these two methods is relevant because, as demonstrated previously [22], PFO administers oxygen more efficiently than CFO and thus may achieve the same $F_{ET}O_2$ using lower average oxygen flow rates. Despite previous studies on the relationship between PFO and CFO, the volume of oxygen PFO should administer for effect equal to CFO is still unknown because previous attempts have reported conflicting results [20, 23–26]. Since the relationship between PFO and CFO is not clear, PFO flow levels must be titrated to each patient [27]. Therefore, this portion of the study attempts to define the ratio between PFO and CFO flow rates in 30 healthy volunteers.

The oxygen sampling system can deliver both PFO and CFO. When administering CFO, the system delivers set oxygen flow rates from 0 to 10 L/min. When administering PFO, the system varies flow rate throughout early inspiration with peak flows as high as 35 L/min. The system then turns flow off during both late inspiration and exhalation. Although PFO peak flows are as high as 35 L/min, the volume of oxygen PFO administers per minute is the same as CFO. When comparing PFO and CFO, the flow rate was calculated as the total volume of oxygen administered per minute, regardless of whether the oxygen reached the alveoli or not. Because only a portion of the oxygen CFO administers reaches the alveoli, CFO obtains lower $F_{ET}O_2$ when administering the same flow rate as PFO.

Various flow rates of pulsed and continuous flow were compared. Since $F_{ET}O_e$ could not be measured directly, it was estimated using the $F_{ET}O_e$ method. To determine if the method's $F_{ET}O_e$ estimates were practical, they were compared to previously published results [28]. In addition, the relationship between flow rate and $F_{ET}O_2$ when administering PFO was determined. After calculating the relationship between flow rate and $F_{ET}O_2$, PFO flow rates equivalent to CFO were calculated. PFO/CFO flow ratios were determined by dividing the PFO flow rates equivalent to CFO by the corresponding CFO flow rates. An overall average PFO-CFO flow ratio was then found by averaging the PFO/CFO flow ratios for each individual flow rate. Data analysis was performed using RStudio (Version 1.1.456, RStudio, Inc., Boston, MA).

3 Results

3.1 Method evaluation

3.1.1 Bench validation

A total of 18 breath washout conditions were evaluated over four breaths per condition (72 data points). The mean difference between backward extrapolated $F_{ET}O_e$ and observed $F_{ET}O_2$ is shown in Fig. 5. The mean differences between

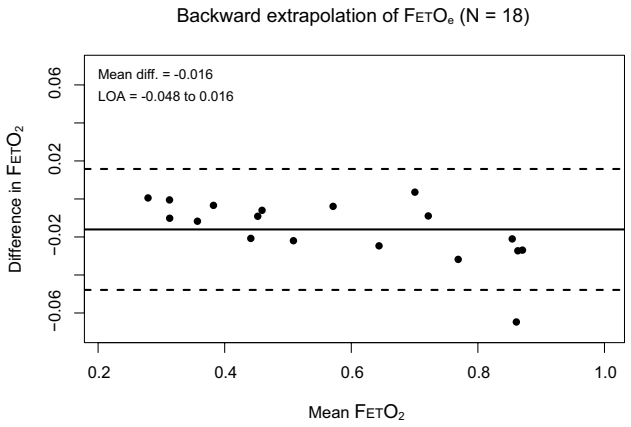

Fig. 5 Bland–Altman analysis for backward extrapolation of the supplemental oxygen enhanced end-tidal O_2 fraction ($F_{ET}O_e$) during bench testing

interpolated and observed $F_{ET}O_2$, as well as between forward extrapolated and observed $F_{ET}O_2$, are shown in Fig. 6.

3.1.2 Volunteer evaluation

Thirty subjects (14 females/16 males; age: 34 ± 12 years, height: 172.4 ± 10.1 cm, weight: 75 ± 17.6 kg, mean ± SD) participated in the volunteer evaluation. 13 breath washouts per volunteer (390 total) were collected. The mean $F_{ET}O_2$ while breathing room air ($F_{ET}O_{air}$) was 0.15 ± 0.01 (SD). Estimated FRC ranged from 2.50 to 3.69 L (3.07 ± 0.37 L, mean ± SD).

Figure 7 shows the calculated and observed measurements and the corresponding absolute errors (calculated minus observed) for a select volunteer. For this particular volunteer, all interpolations were within ± 0.01 FO_2. The largest forward extrapolation error, which is representative of expected errors for $F_{ET}O_e$, was − 0.012 FO_2 (− 1.2% O_2).

The mean difference between interpolated and observed $F_{ET}O_2$, as well as between forward extrapolated and observed $F_{ET}O_2$, are shown in Fig. 8.

3.2 Comparing pulsed and continuous flow oxygen

Thirty subjects (14 females/16 males; age: 34 ± 12 years, height: 172.4 ± 10.1 cm, weight: 75 ± 17.6 kg, mean ± SD) participated in this study. For both PFO and CFO, $F_{ET}O_2$ increased linearly with flow rate (Fig. 9). The linear fit for flow rate in L/min versus $F_{ET}O_2$ during PFO was:

$$\text{Flow rate} = 7.738 \cdot F_{ET}O_2 - 1.33 \left(R^2 = 0.99\right). \quad (4)$$

Equation 4 represents the relationship between flow rate and $F_{ET}O_2$ when administering PFO and can calculate the flow rate required to achieve a specific $F_{ET}O_2$ (Fig. 9). The $F_{ET}O_2$ measured at each CFO flow rate (1, 2, 4, 6, 10 L/min) was put into Eq. 4 to determine the equivalency between PFO and CFO flow rates, where equivalent flow rates obtain the same $F_{ET}O_2$. Equation 4 then gave the PFO flow rate required to achieve that same $F_{ET}O_2$. The equivalent PFO flow rate calculated using Eq. 4 was then divided by the original CFO flow rate used to obtain that $F_{ET}O_2$ to give the PFO/CFO flow ratio.

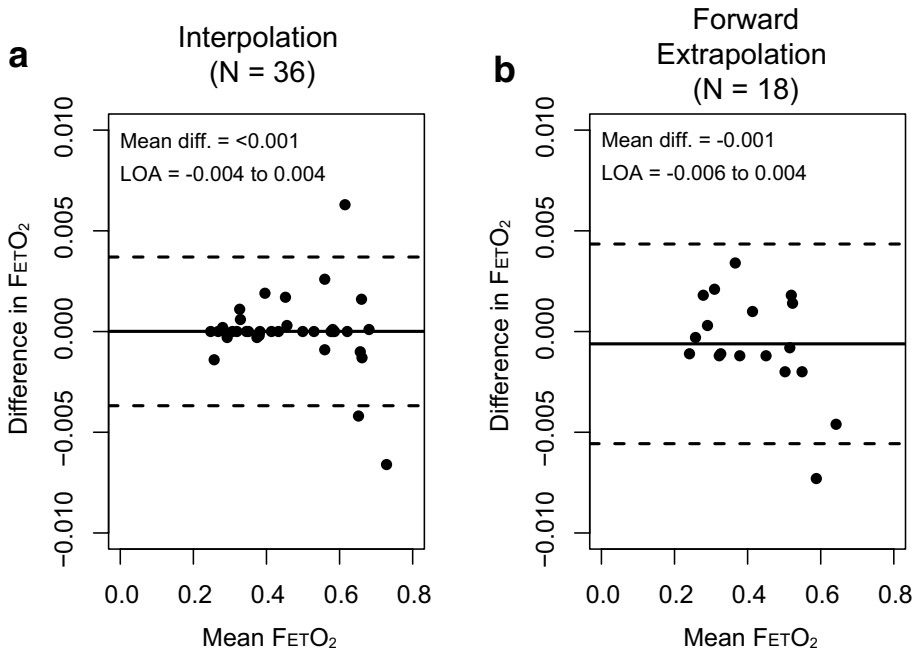

Fig. 6 Bland–Altman analysis for the breath washout end-tidal O2 fractions ($F_{ET}O_2$) during our bench study. **a** The mean difference between and 95% limits of agreement for interpolated and observed $F_{ET}O_2$ washout values **b** the mean difference between and 95% limits of agreement for forward extrapolated and observed $F_{ET}O_2$ values. Note interpolated and forward extrapolated breath values were simulated from Breath 1 $F_{ET}O_2$

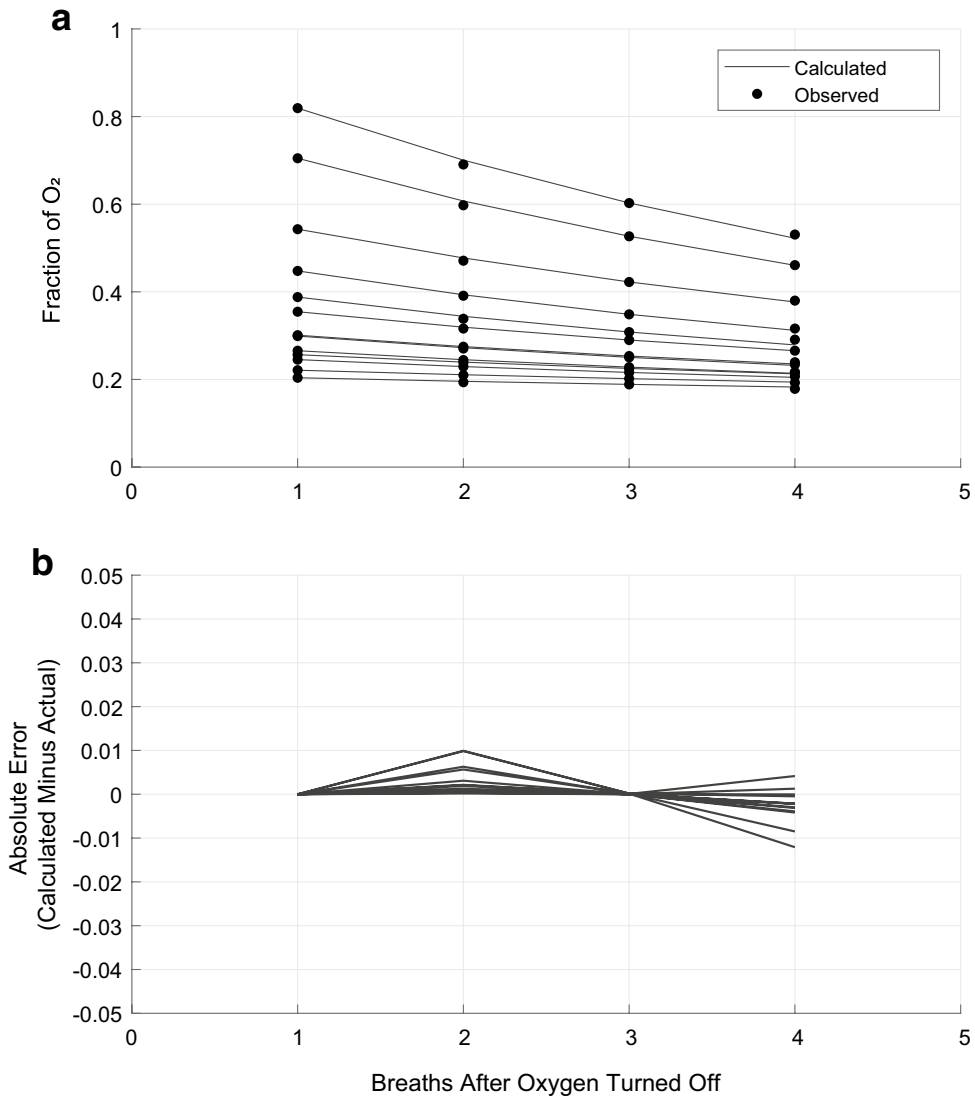

Fig. 7 Inter/extrapolated breath washouts for a single selected volunteer. **a** Comparison of calculated end-tidal oxygen fraction ($F_{ET}O_2$) values (solid lines) with observed values (points) for all $F_{ET}O_2$ measurements. **b** Absolute error (calculated minus observed) of breath washouts for all $F_{ET}O_2$ measurements

The methods' estimates of CFO $F_{ET}O_2$ were all within ± 0.05 FO_2 of previously published measurements obtained using a nasal catheter (See Table 1). Also, Table 1 shows the equivalent PFO flow rates and PFO/CFO flow ratios. PFO achieved $F_{ET}O_2$ values equal to CFO using a mean of 32.1 ± 2.27 (SD) % of CFO flow rates. What that indicates, for example, is that PFO can obtain the same $F_{ET}O_2$ as 10.0 L/min CFO using a flow rate of only 3.21 L/min.

4 Discussion

This paper evaluated and applied a method for estimating nasal $F_{ET}O_2$ enhanced by administering supplemental oxygen. Evaluating the method has shown that mean differences and LOA are clinically insignificant (within ± 0.05 FO_2) when estimating $F_{ET}O_e$ with the method. By applying the method successfully, this paper has also provided the flow rates to use when administering PFO in place of CFO.

The bench study's backward extrapolation of $F_{ET}O_e$ and forward extrapolation of $F_{ET}O_2$ had 95% LOA within ± 0.05 FO_2. In theory, both the mean difference and LOA of backward and forward extrapolation would be similar. They should be similar since the breaths used to calculate the model coefficient are only one breath away from them. Our results showed that the mean difference and LOA were larger for backward extrapolation of $F_{ET}O_e$. For the same washout, $F_{ET}O_e$ values were always higher than forward extrapolation of $F_{ET}O_2$ values. The largest $F_{ET}O_e$ mean differences were observed at $F_{ET}O_2$ values above 0.7, a value higher than any of the forward extrapolated $F_{ET}O_2$ values. Considering $F_{ET}O_e$ was always higher than forward extrapolation, $F_{ET}O_2$ estimates compared well.

Mean differences from the volunteer study showed that the method can estimate $F_{ET}O_e$ with sufficient accuracy for

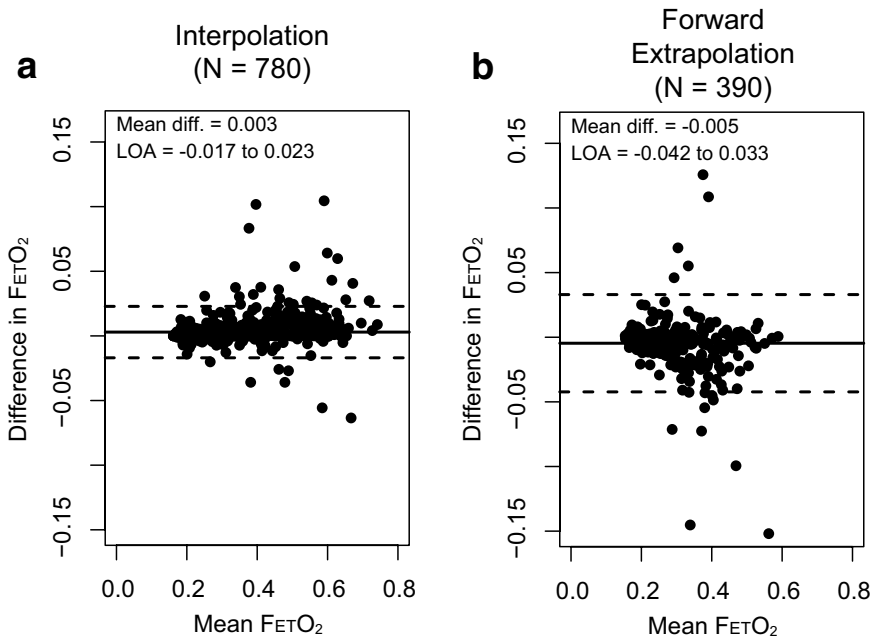

Fig. 8 Bland–Altman analysis for inter/extrapolated end-tidal O2 fraction ($F_{ET}O_2$) in healthy volunteers. **a** The mean difference between and 95% limits of agreement for interpolated and observed $F_{ET}O_2$ washout values **b** the mean difference between and 95% limits of agreement for forward extrapolated and observed $F_{ET}O_2$ values. Note interpolated and forward extrapolated breath values were simulated from Breath 1 $F_{ET}O_2$

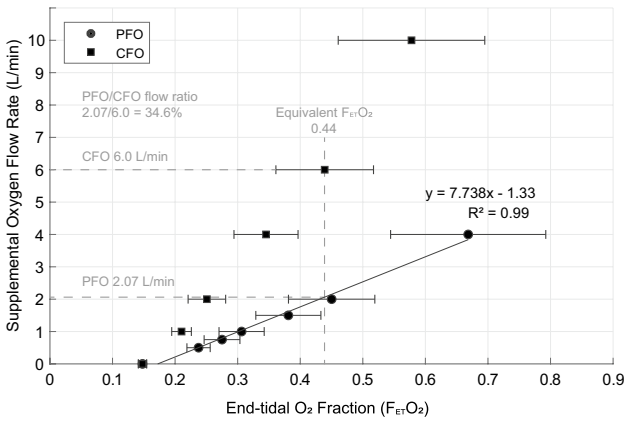

Fig. 9 Comparison of resulting end-tidal oxygen fraction from pulsed (circle) and continuous flow oxygen (CFO, square). Each data point is the mean across all 30 volunteers. Error bars represent standard deviation

clinical use. The mean difference for interpolation during the volunteer study was similar to the bench study while the mean difference for forward extrapolation was larger than the bench study (but still less than 0.01 FO_2). Since on the bench the method estimated $F_{ET}O_e$ with larger mean differences than forward extrapolation of $F_{ET}O_2$, had $F_{ET}O_e$ been measured in volunteers the mean difference would have likely been greater than forward extrapolation of $F_{ET}O_2$. Larger mean differences are expected since volunteer testing evaluated the method across volunteers with a wide range of estimated FRC. Despite this wide range, the method's estimates of interpolated and forward extrapolated $F_{ET}O_2$ agreed well with observed measurements.

The $F_{ET}O_e$ estimated by the method are consistent with previously published results. Wettstein et al. measured FiO_2 with a nasal catheter while administering oxygen via nasal cannula in volunteers [28]. Their measurements agree well with the $F_{ET}O_e$ estimated by the method. Since their measurements and the method's estimates agree, the $F_{ET}O_e$ estimation method may provide a less invasive means for estimating $F_{ET}O_e$ with as much accuracy as a nasal catheter.

Results showed PFO requires only 32.1% as much oxygen volume as CFO. This ratio agrees both with calculations and with previous studies [22, 25, 29, 30]. With a typical I:E ratio of 1:2, inhalation comprises one-third of the respiratory cycle. Based on this calculation PFO would only require one-third as much oxygen volume, a value well within range of the results. Other studies have reported similar PFO/CFO flow ratios of ~40% [22, 25, 29, 30]. Given that these studies were performed during rest, exercise, and sleep, they further support the method for estimating $F_{ET}O_e$.

The $F_{ET}O_e$ method is best suited for estimating $F_{ET}O_2$ during regular, rhythmic breathing. Estimates may be less accurate during depressed breathing when expiratory pause times are longer, and when oxygen consumption varies breath-by-breath. This is because the model only adjusts for the oxygen that the mixing of FRC and Vt extracts from the lung but does not consider the oxygen that metabolic oxygen consumption removes from the lung.

The model's accuracy will depend on the consistency and size of Vt throughout the breath washout. If Vt varies substantially, the model coefficient doesn't represent the breath washout, and the method will calculate $F_{ET}O_2$ less accurately. Since the method is based on extrapolation, it may be less functional in cases of low Vt and high respiratory rate. This

Table 1 PFO equivalent flow rate and PFO to CFO flow ratio observed in healthy volunteers (N = 30)

CFO set flow (L/min)	Wettstein et al. CFO $F_{ET}O_2$[a]	CFO $F_{ET}O_2$	PFO equivalent flow rate (L/min) PF rate = 7.738 · CFO $F_{ET}O_2$ − 1.33	PFO/CFO flow ratio (%)
1	0.18	0.21 ± 0.02	0.30	30.0
2	0.24	0.25 ± 0.03	0.60	30.0
4	0.34	0.35 ± 0.05	1.38	34.5
6	0.42	0.44 ± 0.08	2.07	34.5
10	0.53	0.58 ± 0.12	3.16	31.6

Previously published results from the study of Wettstein et al. are included for comparison between CFO $F_{ET}O_2$ [28]

Data are expressed as Mean ± SD

CFO continuous flow oxygen, *PFO* pulsed flow oxygen, $F_{ET}O_2$ end-tidal O_2 fraction

[a]The manuscript of Wettstein et al. reported FiO_2 values. $F_{ET}O_2$ was calculated from the FiO_2 data by subtracting an estimated difference of FiO_2–$F_{ET}O_2$ = 0.21 − 0.15 = 0.06 from FiO_2 values

means the method will estimate $F_{ET}O_e$ less accurately in the subset of patients that require supplemental oxygen and have a high respiratory rate.

The results from comparing PFO and CFO presented here are limited to a healthy volunteer population with regular respiratory rate. Populations with lower respiratory rates, such as sedated surgical patients, could have a different ratio of PFO/CFO flow rates.

If oxygen is discontinued precisely in sync with the start of exhalation, nasal $F_{ET}O_2$ may represent $F_{ET}O_e$ if sampled immediately after discontinuing oxygen. However, this would require sampling of nasal gas during oxygen delivery since gas sampling misses the first $F_{ET}O_2$ when switched from off to on. Typically, a FiO_2 of 0.21 after turning off oxygen flow causes erroneously low FEO_2 measurement. Thus, $F_{ET}O_2$ measured after discontinuing flow normally does not represent $F_{ET}O_e$.

The method for estimating $F_{ET}O_e$ is useful when administering CFO and when gas is sampled at a high rate relative to oxygen flow. When administering PFO, directly measuring $F_{ET}O_e$ may be more accurate than estimating $F_{ET}O_e$, as a previous study has demonstrated that nasal end-tidal carbon dioxide can be measured accurately during PFO [31, 32]. Since end-tidal carbon dioxide is distorted during oxygen flow but can be measured accurately during PFO, measuring other end-tidal gases, including oxygen, may also be accurate during PFO.

Recent studies have shown that preoxygenating with a nasal cannula is feasible and safe [33, 34]. Until now, these studies have shown feasibility by measuring SpO_2 and the partial pressure of oxygen in the arterial blood (PaO_2). Estimating $F_{ET}O_e$ may provide an additional means to assess the feasibility of preoxygenating using a nasal cannula.

In summary, this paper has demonstrated a method for estimating $F_{ET}O_2$ enhanced by administering supplemental oxygen. The method estimated $F_{ET}O_e$ with clinically insignificant differences. This paper has also shown an example of how to apply this method by demonstrating in healthy volunteers that PFO can obtain $F_{ET}O_2$ values similar to CFO using approximately one-third of the oxygen volume. After evaluating this method, we conclude that the method provides useful estimates of nasal $F_{ET}O_2$ enhanced by supplemental oxygen administration.

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Compliance with ethical standards

Conflict of interest Kyle Burk: Dynasthetics LLC. Kai Kuck: No Conflict of Interest. Joseph Orr: Dynasthetics LLC.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human and animal rights This article does not contain any studies with animals performed by any of the authors.

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