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ORIGINAL RESEARCH

FiO_2 prediction formula during low flow oxygen therapy in an adult model: a bench study

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Abstract

During low-flow oxygen therapy, the true value of inspired oxygen fraction (FiO_2) is generally unknown. Knowledge of delivered FiO_2 values may be useful as well as to adjust oxygen therapy, as well as to predict patient deterioration. This study proposes a New FiO_2 Prediction Formula ($NFiO_2$) for low-flow oxygenation and compares its predictive value to precedent formulas. In a bench study, the O_2 Flow rate was delivered through a T-piece connected to a dual-compartment artificial lung controlled by a mechanical ventilator. To test the $NFiO_2$ formula, a set of ventilatory parameters were tested: Tidal Volume was set from 400 to 600 ml, Respiratory Rate (RR) was set from 18 to 30 CPM, Ti/Ttot was set at 0.33 and 0.25, and O_2 flow rates from 3 to 10 L/min. A data acquisition system measured all parameters. To quantify the accuracy of the $NFiO_2$ compared to other FiO_2 prediction formulas, Bland and Altman agreement analyses were performed. To make use of the Duprez Formula 2018 in clinical practice, we simplified the formula to estimate the FiO_2 during oxygenation at low flow. This $NFiO_2$ formula makes use of only O_2 Flow Rate and RR. Bias and limits of agreement between predicted FiO_2 and benchtop FiO_2 highlighted consistent differences between different FiO_2 prediction formulas. The $NFiO_2$ and the Duprez Formula 2018 seemed to be the most accurate formulas, followed by the Vincent Formula, and lastly the Shapiro Formula. A New FiO_2 Prediction Formula was developed using clinical readily available variables (RR and O_2 Flow rate) which showed good accuracy in predicting FiO_2 during oxygenation at low flow.

Keywords Prediction formula · FiO_2 · Low flow oxygen therapy · Hypoxemia · Hypoxia

1 Background

Oxygen therapy is the principal treatment of hypoxemia. Oxygen administration should be closely monitored and adapted to the patient's clinical conditions during therapy. Knowledge of delivered FiO_2 values may be useful as well as to adjust therapy, as well as to predict patient deterioration. During low-flow oxygen therapy (usually administered through a nasal cannula), FiO_2 values are generally unknown or difficult to estimate [1]. For many years, to estimate FiO_2, various formulas, based on theoretical reasoning, have been proposed. The two mainly used formulas to estimate FiO_2 at low flow are the Vincent and Shapiro Formulas [2–6].

Both formulas estimate FiO_2 on the amount of delivered O_2 Flow only. However, at low-flow, FiO_2 will depend on the mixture of inspired air (at 21% of oxygen) by the patient and the delivered O_2 Flow by the system [5–7]. Therefore, FiO_2 will greatly depend on the patient's breathing pattern [8]. Thus, in 2018, based on a bench study, we proposed a formula to predict FiO_2 during oxygenation at low flow (Duprez

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Formula 2018). This formula considers: O_2 Flow, Minute Ventilation (MV) and Ti/Ttot ratio [4]. While encompassing inspiratory flow, Duprez Formula 2018 has been shown to greatly increase FiO_2 prediction accuracy compared to former FiO_2 prediction formulas. Unfortunately, Duprez Formula 2018 remains of limited clinical use because the value of MV and Ti/Ttot ratio are unknown during low-flow oxygen therapy. Therefore, this study aims:

(1) To simplify the Duprez Formula 2018 in a New Formula that only uses bedside readily available variables (i.e. RR and $LPMO_2$).
(2) To test the predictive performance of this new formula experimentally.
(3) To compare the accuracy of this new formula against the precedent formulas.

2 Methods

2.1 Part 1: theoretical simplification of the Duprez Formula 2018

The original Duprez Formula 2018 is equal to:

$$FiO_2 = 0.21 + 0.79 \times \left(\frac{Ti}{Ttot}\right) \times \left(\frac{LPMO_2}{MV}\right)$$

Ti—Inspiratory time (sec), Ttot—Total breathing cycle (sec), LPM O_2: Oxygen Flow Rate (L/min), MV—Minute Ventilation (RR×Vt), Vt—Tidal Volume (L), RR—Respiratory Rate (CPM).

The first development of the new FiO_2 Formula is based on the hypothesis that the Vt of a resting adult varies approximatively between 0.4 and 0.6 L [9]. We therefore replaced Vt with a mean value of 0.5 L. The Duprez Formula 2018 can be rewritten as:

$$FiO_2 = 0.21 + 0.79 \times \left(\frac{Ti}{Ttot}\right) \times \left(\frac{LPMO_2}{MV}\right)$$

$$\text{with:} MV = Vt \times RR$$

$$FiO_2 = 0.21 + 0.79 \times \left(\frac{Ti}{Ttot}\right) \times \left(\frac{LPMO_2}{Vt \times RR}\right)$$

$$\text{with:} Vt = 0.5L$$

$$FiO_2 = 0.21 + 0.79 \times \left(\frac{Ti}{Ttot}\right) \times \left(\frac{LPMO_2}{0.5 \times RR}\right)$$

or simplified:

$$FiO_2 = 0.21 + 1.58 \times \left(\frac{Ti}{Ttot}\right) \times \left(\frac{LPMO_2}{RR}\right)$$

As the $\frac{Ti}{Ttot}$ ratio is unknown in clinical practice, a new constant (k) must be found:

$$k = 1.58 \times \left(\frac{Ti}{Ttot}\right)$$

This simplifies the formula as follow:

$$FiO_2 = 0.21 + k \times \left(\frac{LPMO_2}{RR}\right)$$

Since Duprez Formulas 2018 were proposed for two Ti/Ttot (0.25 and 0.33), this constant (k) should vary between ± 0.40 and ± 0.50 respectively, (more easily used as $\frac{1}{k}$ and thus ± 2.5 to ± 1.9)

2.2 Part 2: Experimental set-up

(1) To determine a new constant (k) value:

$$k = (FiO_2 - 0.21) \times \frac{RR}{LPMO_2}$$

(2) To test the New FiO_2 Prediction Formula

$$FiO_2 = 0.21 + k \times \left(\frac{LPMO_2}{RR}\right)$$

The parameters analyzed on bench were:

- Ti/Ttot: 0.25 and 0.33
- LPM O_2: from 3 to 10 L/min (step: 1 L/min)
- Vt: 0.4/0.5/0.6 L
- RR: 18/22/26/30 CPM

Spontaneous breathing was generated with a mechanical test lung (Dual Test Lung—Michigan Instruments, Inc. Grand Rapids Model 5600i) including two independent experimental lungs. With a special coupling clip, the first lung is used to drive the second lung in order to achieve a breathing simulation (inspiratory and expiratory flow). The settings of the experimental lung were: resistance: ± 5 cm H_2O/L/sec and compliance ± 0.06 L/cm H_2O. The first lung was connected to a mechanical ventilator Servo-i® set to volume control mode with descending ramp flow waveform (25%), time pause and inspiratory rise time at 0%, peep of 0 cm H_2O, the trigger was set at − 15 cm H_20 in order to avoid self-triggering. O_2 Flow rate from a wall-mounted Thorpe Tube (Air Liquide™ RTM3; 0 to 15 L/min) was delivered through a T piece (with a very small material dead space).

The T piece was directly fixed to the flow sensor (Fig. 1). An O_2 analyzer was located of the O_2 port of the second lung.

The main outcome variable was FiO_2 (expressed as the volumetric percentage of O_2 in the steady-state experimental lung). FiO_2 was measured with a GA-200, O_2 Gas Analyzer (Iworx®, United States). The O_2 Monitor was calibrated with air room (21%) then at 100% with certified O_2 gas. FiO_2 was measured as the mean of 10 breaths after a stabilization period of at least one minute.

To test the predictive value of the New FiO_2 Prediction Formula ($NFiO_2$) across different breathing patterns and experimental settings, we defined 1080 (3 × 360) experimental set-ups by modifying different parameters: O_2 Flow, Vt, Respiratory rate (RR), and the ratio between inspiratory time (Ti) upon the total breathing cycle (Ttot).

Ti/Ttot, Tidal Volume, and RR were measured with a data acquisition system IX-214 (Iworx®, United States) which included an SP-304 flow sensor and a data-acquisition hardware connected to a Software Labscribe 3™ (Iworx®, United States). The flow sensor was calibrated using a 1-liter calibration syringe (Hans Rudolph 5540™—United States) and ambient air. During this step, the gap between the required value and measured value was of maximum ± 30 mL.

O_2 Flow was measured continuously with a Thermal O_2 Mass Flow Meter (Red Y Vögtlin™ Instruments GmbH, Switzerland: Accuracy ± 1.5% of full scale/ Repeatability +/– 0.1% of full scale). Because the accuracy of measurements could become aleatory at very low flow, only the O_2 Flows rate from 3 to 10 L/min were measured.

During the experiment, all measurements were performed in triplicate with recalibration on each occasion. Each experiment was blinded for previously obtained results to avoid a Pygmalion effect.

2.3 Part 3: comparison of the $NFiO_2$ accuracy against precedent formulas

The following formulas were analyzed:

Duprez Formula 2018: $FiO_2 = 0.21 + 0.79 \times \left(\frac{Ti}{Ttot}\right) \times \left(\frac{LPMO_2}{MV}\right)$

Vincent Formula: $FiO_2 = 0.21 + \left(0.03 \times LPMO_2\right)$

Shapiro Formula: $FiO_2 = 0.20 + \left(0.04 \times LPMO_2\right)$

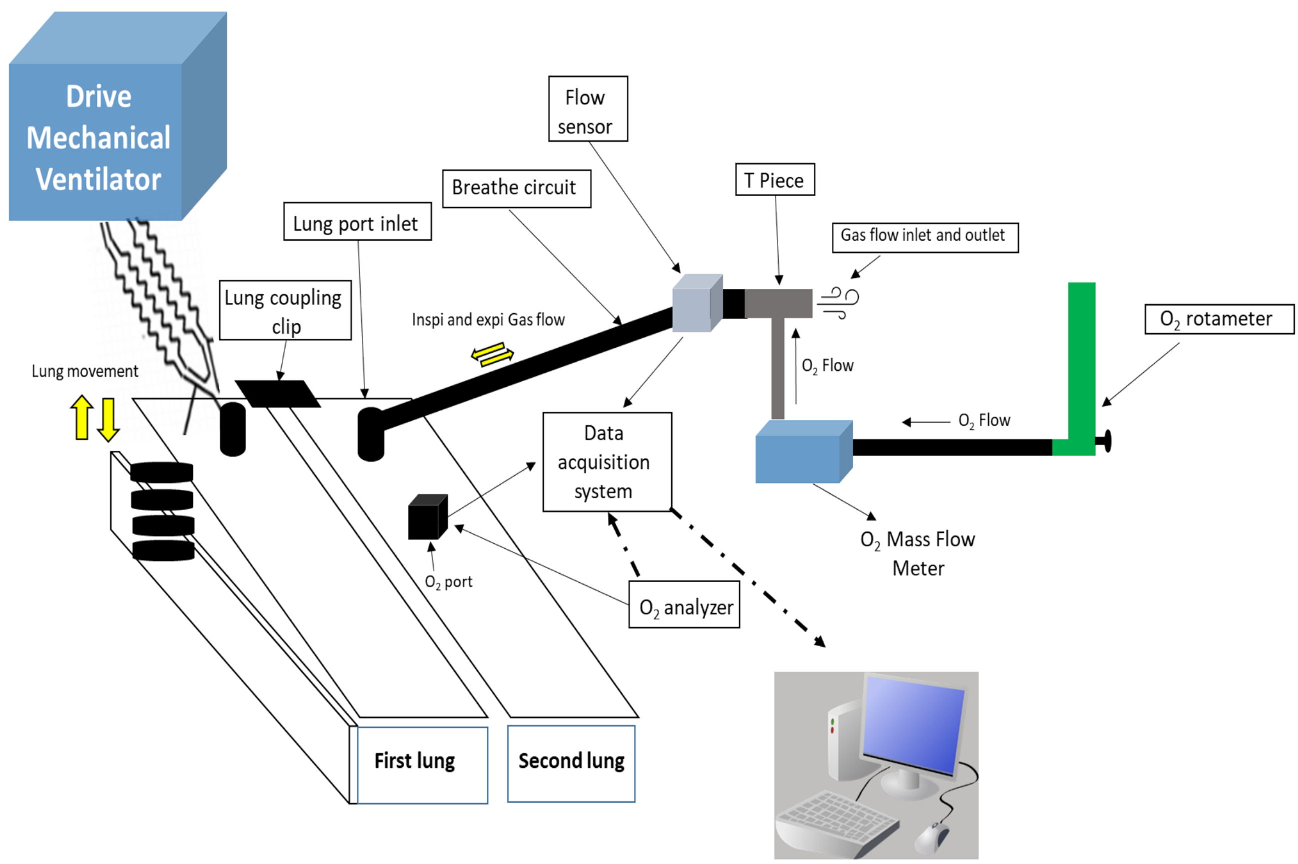

Fig. 1 Set-up of the experimental adult bench model

2.4 Statistical analysis

Data were analyzed using Sigma Plot Software (Version 14.0 Systat Software Inc, UK). Mean values are expressed with their standard deviation. The repeatability of the Thermal O_2 Mass Flow Meter and the SP-304 Flow Sensor was conducted by using the intraclass correlation coefficient (two-way mixed effects, absolute agreement, single rater, multiple measurements) [10].

- Determination of the new constant (k):
  - Computing the mean value of "k" across the different experimental set-ups.
  - Using the Bland and Altman method [11], (computation of the agreement between the FiO_2 calculated by the $NFiO_2$ and the measured FiO_2 obtained on the bench) different constant (k) values were tested to predict the most adequate FiO_2. The following constants (k) were tested: from 0.40 to 0.55.
- $NFiO_2$ comparison against precedent formulas.

To compare the accuracy of $NFiO_2$, we analyzed the FiO_2 obtain for each experimental set-up (n = 360) and compare it with other prediction formulas: Duprez Formula 2018, Vincent and Shapiro Formulas [2, 3].

As such, the bias (measured FiO_2—predicted FiO_2), the standard deviation (SD), and the Limits of Agreement (LoA) are reported for each prediction formula with their 95% confidence interval.

3 Results

The intraclass correlation coefficient of the O_2 mass flow meter and SP-304 were > 0.90 ($p < 0.01$), respectively. The repeatability of experimental measurements was excellent.

Throughout the different experimental set-ups, the mean constant (k) value was 0.53 (SD 0.10). Therefore, for ease of use, the constant (k) value was rounded up to 0.5 and simplifies the FiO_2 prediction formula as follow:

$$FiO_2 = 0.21 + 0.5\left(\frac{LPMO_2}{RR}\right)$$

or

$$FiO_2 = 0.21 + \left(\frac{LPMO_2}{2 \times RR}\right)$$

Meanwhile, different constants (k) were used and tested (Table 1). The constant k that showed the best agreement between calculated FiO_2 and measured FiO_2 using a Bland and Altman analysis was 0.53.

Compared to the other formulas, the bias and range of LoA were lowest for the $NFiO_2$ (− 1.33/− 6.95 to 4.29) and Duprez Formula 2018 (− 3.61/− 8.68 to 1.46), followed by the Vincent Formula (4.15/− 4.65 to 12.96), and last by the Shapiro Formula (9.69/− 2.44 to 21.81) (Fig. 2; Table 2).

4 Discussion

At first, we simplified the Duprez Formula 2018 to estimate the FiO_2 during oxygenation at low flow using clinical readily available variables i.e. $LPMO_2$ and RR. The former Duprez Formula 2018 did indeed include variables (VM and $\frac{Ti}{Ttot}$) that are unknown in clinical practice under low flow oxygen therapy and thus preventing its practical use. This experimental bench study could identify a new constant (k = 0.5 or 1/k = 2) value, encompassing unknown respiratory variables, that has allowed to reformulate the former Duprez 2018 formula as follow:

$$FiO_2 = 0.21 + 0.5 \times \left(\frac{LPMO_2}{RR}\right) \text{ or } FiO_2 = 0.21 + \left(\frac{LPMO_2}{2 \times RR}\right)$$

Despite this simplification, this formula did show to be robust even after comparison to the former Duprez Formula 2018 but also in comparison to previously used formulas (Shapiro and Vincent).

In our analysis, consistent differences were shown between prediction formulas. To estimate FiO_2 during oxygenation at low flow, the $NFiO_2$ and the Duprez Formula 2018 seemed to be the most accurate formulas, followed by the Vincent Formula, and lastly the Shapiro Formula.

For the Duprez Formula 2018 and $NFiO_2$, if the minute ventilation (and/or RR) increases or Ti/Ttot decreases, then FiO_2 decreases, and vice versa [12]. Therefore, following our experiences, the inspiratory flow rate (i.e., minute ventilation divided by Ti/Ttot) and the oxygen flow rate are the main parameters that determine the FiO_2 value during oxygenation at low flow rate. Meanwhile, the Vincent

Table 1 Bias, standard deviation for "1/k" value simulation of $NFIO_2$ prediction formula

"1/k" value simulation	1.8	1.9	2	2.1	2.2	2.3	2.4	2.5
Bias	− 0.2	1	− 1.3	− 2	− 2.6	− 3.2	− 3.69	− 4.2
SD	3.2	3	2.9	2.8	2.7	2.6	2.6	2.6

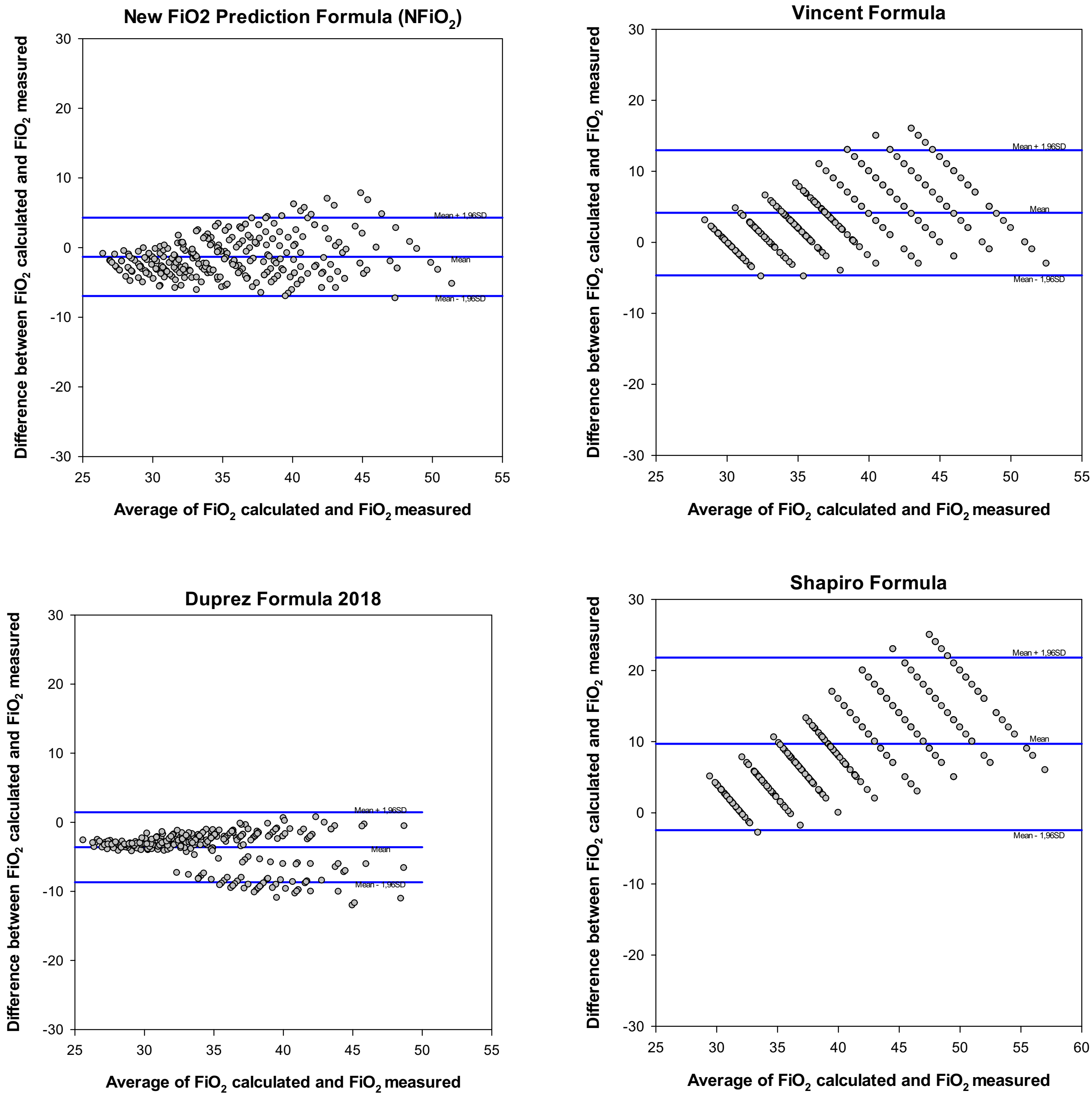

Fig. 2 Bland–Altman plots comparing expected FiO_2 values (obtained by calculation with the $NFiO_2$, the Duprez formulas, Vincent Formula, and Shapiro Formula) with measured FiO_2 (for O_2 Flow ranging from 3 to 10 L/min, RR from 18 to 30 cpm, Tidal Volume from 400 to 600 mL, Ti/Ttot = 0.25 and Ti/Ttot = 0.33)

and Shapiro Formulas do not include Minute Ventilation and Ti/Ttot ratio in their prediction formulas. This may be the reason why these formulas are less accurate. As for example, if O_2 Flow is equal to 6 L/min and the RR is equal to 30 CPM, Shapiro FiO_2 estimation, will predict an FiO_2 of 44%, and the Vincent Formula will predict an FiO_2 of 39%. With the $NFiO_2$, the calculation will give a FiO_2 value of 31%, either an absolute FiO_2 difference of 13% and 8% between the former formulas and the $NFiO_2$. Sometimes, in emergency situations, for a short period, the oxygen flow of oxygen through traditional nasal cannulas can exceed 6 L/min [13–15]. In this case, in patients with relatively high oxygen flow and high RR, the prediction of FiO_2 with formula which do not take into account variables related to the Minute Ventilation (such as RR) could lead to an incorrect assessment of the degree of

Table 2 Bias, standard deviation, limits of agreement, range of limits agreement for each prediction formulas

	Duprez formula 2018	New FiO_2 prediction formula (with "k" = 0.5)	Vincent Formula	Shapiro Formula
Bias	−3.61	−1.33	4.15	9.69
SD	2.58	2.87	4.49	6.19
Limits of agreement (Range)	−8.68 to 1.46 (10.14)	−6.95 to 4.29 (11.24)	−4.65 to 12.96 (17.6)	−2.44 to 21.81 (24.25)

All values are expressed in percentage of FiO_2

hypoxemia. For example, if the Oxygen flow reach 10 L/min and RR of 30 cpm, the FiO_2 calculation with Shapiro Formula reach 60%, with Vincent Formula: 51% and 38% for $NFiO_2$ either an absolute FiO_2 difference of 22% and 13%. Nevertheless, when the Vt is around 500 mL and the RR around ± 15 CPM, the Vincent Formula seems adequate to accurately predict the FiO_2 at low flow. The application of FiO_2 prediction in low oxygenation with the New FiO_2 Prediction Formula presented in this bench study should be further studied in clinical practice.

Beyond these considerations, it is of clinical interest to bring to the fore a standardized common denominator of the amount of oxygen a patient receives, such as FiO_2. Given known factors affecting FiO_2, formulas to determine FiO_2 should be defined for each oxygen delivery device and adjusted for oxygen flow and the patient's breathing pattern [16]. The present work illustrates that even in low-flow oxygen delivery settings, to enhance accuracy, it is important to integrate a breathing parameter, in this case, the RR, to estimate and adjust FiO_2. Hence, FiO_2 should be more accurate in specifying the degree of hypoxemia and, thus, oxygenation needs of a patient than specifying oxygen flow alone. Using such a unique denominator across different oxygen delivery devices has, in our opinion, different clinical impacts and advantages:

- It could simplify communication between colleagues (between wards or institutions) regarding one patient's oxygen needs.
- It can facilitate and simplify data encoding and processing in electronic health records.
- It could facilitate research work, such as severity score calculations.

In this era of big data analysis, using an adjusted FiO_2 will be more reliable than encoding, processing, and interpreting amounts of oxygen delivered through different devices. Ultimately, it could therefore facilitate automatic electronic severity score calculations through the electronic medical interfaces and software and adjust alarm settings for patients' safety.

5 Limitations

First, given our experimental design, the New FiO_2 Prediction Formula should be limited to an oxygen flow between 3 and 10 L/min (without material dead space), a RR between 18 and 30 CPM, two Ti/Ttot (0.25 and 0.33) and a Vt between 400 mL and 600 mL respectively (either adult conditions). Second, a patient's tidal volume and inspiratory flow can vary from breath to breath. In this case, the FiO_2 for a given breath can sometimes be difficult to predict [17]. Third, the effect of open mouth (or not) on FiO_2 has not been evaluated and could result in a variation of FiO_2 from previous bench results [6]. Finally, due to the bench study, we did not consider the effect of anatomical dead space on the FiO_2. For this reason, it is possible that the FiO_2 value itself differs slightly from that of real humans.

6 Conclusion

FiO_2 assessed during low flow rate oxygen therapy in a spontaneous breathing lung model and compared to four FiO_2 prediction formulas shows larger differences. This bench study highlights, compared to former prediction formulas, that the New FiO_2 Prediction Formula for low-flow oxygen therapy, based on RR and oxygen flow rate, shows better accuracy in predicting FiO_2.

This bench study highlights that including RR to oxygen flow rate in a FiO_2 prediction formula at low flow may enhance accuracy compared to formulas including solely oxygen flow rate. Although many parameters influence FiO_2, this study confirms that respiratory frequency influences FiO_2 in an inversely proportional manner.

Author contributions FD: conception experiment+wrote the main manuscript. BM experimentation+wrote the main manuscript. BL: conception of the experiment+wrote the main manuscript. MCM: Corrections and review. JBM: Corrections+wrote the main manuscript. SM: Corrections+conception. CD: Corrections, mathematical

approach+wrote the main manuscript. All authors reviewed the manuscript.

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Data availability On demand.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Not applicable.

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