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Oxygen injection sites: Important factors that affect the fraction of inspired oxygen during non-invasive positive pressure ventilation

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ABSTRACT

Background: Most portable bi-level positive airway pressure (BPAP) devices are not equipped with air-oxygen blenders for precisely regulating oxygen concentrations and supplemental oxygen must be added to increase the fraction of inspired oxygen (FiO_2). Very few studies have investigated the factors that affect FiO_2 and their conclusions were inconsistent. We investigated *in vitro* non-invasive positive pressure ventilator (NPPV) parameters and their effects on FiO_2, particularly the effect of the oxygen injection site.

Methods: NPPV therapy in the spontaneous breathing mode was simulated using a simulation lung platform. FiO_2 was measured after varying different parameters: oxygen injection site (mask, in front of exhalation valve, at the humidifier outlet, or proximal to the ventilator); exhalation valve type; oxygen flow; and inspiratory and expiratory pressures. General linear models were used to assess the effects of these experimental factors on oxygen concentration.

Results: The 4 variables of oxygen flow rate, inspiratory and expiratory pressure, and exhalation valve type, all affected the FiO_2. Remarkably, for a given oxygen flow rate, the oxygen injection site was the most important factor that affected FiO_2; an oxygen injection site that was closer to a patient resulted in a higher FiO_2. The highest fraction of inspired oxygen was measured when the oxygen injection site was on the mask (P-values < 0.0001).

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Conclusion: Among the various factors evaluated in this study, for a given oxygen flow rate, the oxygen injection site had the greatest effect on inspired oxygen concentration during NPPV.

Key words: inspired oxygen concentration, noninvasive positive pressure ventilation, respiratory flow rate, oxygen injection site.

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Abbreviation List

FiO_2: fraction of inspired oxygen

NPPV: non-invasive positive pressure ventilation

PEEP: positive end-expiratory pressure

PEV: plateau exhalation valve

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INTRODUCTION

The use of non-invasive positive pressure ventilation (NPPV) has increased dramatically during the last 10 years.[1-3] NPPV is an effective therapy for treating acute respiratory failure that can arise during acute exacerbations of chronic obstructive disease, acute cardiogenic pulmonary edema, and in immuno-compromised patients. It is also a means of weaning patients from endotrachial intubation.[1-3] Ventilator support provides relief for respiratory muscles, increases ventilation and reduces dyspnea and the respiratory rate, and improves arterial oxygenation.[1]

Most patients who are treated with NPPV require supplemental oxygen to maintain appropriate arterial oxygenation. However, many specialized ventilators for NPPV are not equipped with air-oxygen blenders for precisely regulating the amount of oxygen that is delivered to the patient. Thus, ensuring that the appropriate fraction of inspired oxygen is delivered can be difficult.[4-6]

There are numerous factors that can affect the amount of oxygen delivered to a patient and the interactions among these factors are complex. These include: (1) patient factors, such as respiratory drive, respiratory rate, airway resistance, and lung compliance; (2) ventilator parameters, such as oxygen flow, inspiratory/expiratory pressure, and the oxygen injection site; and (3) clinically controllable factors, which are often chosen based on the experience of the medical staff, such as the oxygen injection site and the exhalation

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valve used. Very few studies have investigated what factors influence the fraction of inspired oxygen during NPPV and some of their conclusions were inconsistent, particularly with regard to oxygen injection sites.[7-10] This was possibly due to different experimental designs (human vs. in vitro studies) and/or using different types of equipment, particularly with regard to the response times of oxygen sensors. Also, no studies have investigated the extent to which these various factors affect the fraction of inspired oxygen that can be delivered.

Thus, we performed in vitro experiments to more thoroughly and systematically investigate some of these factors and their effects on the fraction of inspired oxygen during NPPV. These included oxygen flow rate, oxygen injection site, inspiratory/expiratory pressure, and the type of exhalation valve. In addition, we used an oxygen sensor with a rapid response time (300 ms) and software of our design, which significantly facilitated accuracy of oxygen concentration determinations.

METHODS

Simulation lung platform

For simulation experiments, we used a dual-chamber Michigan lung (Adult TTL 1600, MI Instruments, Grand Rapids, MI, USA). As shown in Figure 1, the driver chamber was connected to a ventilator (PB840, Puritan Bennett, Mansfield, MA, USA). The test

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chamber was connected to a portable bi-level positive airway pressure (BPAP) support system (Synchrony, Respironics, Andover, MA, USA) at the facial mask of a head model using a 1.8 m one-way breathing circuit (312107, Respironics, Andover, MA, USA). The connections between the tubing and mask were tight, and the junctions between the face mask and head were filled with silicone patches. The entire breathing loop had no unintentional leaks.

A gas analyzer (VT-Plus, Fluke, Everett, WA, USA) and a recording module of our design were connected in series with the breathing circuit between the facial mask and the test chamber. The breathing circuit was attached to an empty humidifier canister. Rhythmical changes in the driver chamber volume that simulated spontaneous human breathing were transduced to the test chamber through a metal rod. The driver chamber triggered the non-invasive ventilator during early inspiration. Once a breath was triggered, test chamber inflation was controlled by pre-set parameters; test chamber compliance and airway resistance and auto-triggering or missed triggers were not observed at all experimental levels.

Compliance was set to 0.05 L/cmH_2O and resistance was set with a parabolic airway resistor (5 cmH_2O • L^{-1} • sec^{-1}, Pneuflo resistor Rp5; MI Instruments, Grand Rapids, MI, USA) with a resistance of 4.3 cmH_2O • L^{-1} • sec^{-1} at a flow rate of 60 L/min. An oxygen flow meter was connected to a 50 psi wall oxygen source and oxygen was delivered

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at different sites through an extension tube with a three-way adapter.

Experimental conditions

The PB840 ventilator was set in the volume control mode (tidal volume: 500 ml; peak flow rate: 50 L/min; waveform: square-wave). The portable bi-level positive airway pressure (BPAP) support system was set in the spontaneous breathing mode with a pressure rise slope of 3. For all experiments, the PEEP level of the PB840 ventilator was maintained at the same expiratory pressure as the non-invasive ventilator to ensure simultaneous triggering.

The experimental conditions were: (1) inspiratory and expiratory pressures of the portable bilevel positive airway pressure ventilator were adjusted to 15/5, 15/10, 25/5, and 25/10 cmH_2O; (2) exhalation valves included a single-arch valve (Respironics, Andover, MA, USA), a plateau exhalation valve (PEV) (Respironics, Andover, MA, USA), and a mask valve (leak port in the mask) (Respironics, Andover, MA, USA); (3) oxygen flow rate was adjusted to 5and 10 L/min; and (4) the oxygen injection site was placed either proximal to the ventilator, at the humidifier outlet, proximal to the exhalation valve, or on the mask.

Oxygen concentration measurements

Prior to each experiment, to reduce error and ensure experimental reproducibility, the VT-PLUS gas analyzer recorded baseline fluctuations in flow rate and pressure. Each time

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an experimental condition was changed, measurements were compared with the baseline fluctuation range. If the difference was too large, the cause of the difference was corrected and values were measured again. For each new experimental condition, a minimum of 3 min of stabilization time was included prior to the next oxygen concentration measurement.

Oxygen concentration was measured in real time using an oxygen sensor (Oxygen Sensor OOM109/OOM109-LF2; EnviteC-Wismar GmbH-by Haneywell; Wismar, Germany) for which the response time for a 90% change was 300 ms. Inspiratory flow rate was continuously monitored with a flow sensor at a sampling frequency of 30 ms. The inspiratory phase was identified from the flow waveform. Software of our design was used to multiply the real-time oxygen concentration by the inspiratory flow rate at each sampling point of the inspiratory phase. The delivered oxygen volume and the tidal volume were determined by mathematical integration. As shown in Figure 2, the delivered oxygen volume was divided by the tidal volume to determine FiO_2. FiO_2 of the inspiratory phase was calculated using data from three breathing cycles under the various experimental conditions.

Statistical analysis

Results for FiO_2 are given as means ± SDs. Comparisons of FiO_2 concentrations among the different oxygen injection sites under a given experimental condition were made by analysis of variance (ANOVA) with a Bonferroni correction for type I error adjustment

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when multiple comparisons were made. A general linear model was used to assess the effect of each experimental factor on FiO_2 after adjusting for other experimental factors. The adjusted mean differences and corresponding 95% confidence intervals (CI) were calculated from the general linear model. To assess the independent contribution of each experimental factor on FiO_2, F-tests using type III sums of squares (SS) were used. Statistical analyses used SAS software version 9.2 (SAS Institute Inc., Cary, NC). A two-tailed *P*-value of < 0.05 was considered significance.

RESULTS

Figure 3 shows the measured FiO_2 results for different experimental conditions in single arched valve. Figure 4 shows the measured FiO_2 results for different experimental conditions in plateau exhalation valve. Figure 5 shows the measured FiO_2 results for different experimental conditions in mask valve. These conditions included: (1) different oxygen injection sites; (2) 4 combinations of inspiratory/expiratory pressure (panel A:15/5 cmH_2O; panel B: 15/10 cmH_2O; panel C: 25/5 cmH_2O; and panel D 25/10 cmH_2O); and (3) 2 levels of oxygen flow rate (5 and 10 L/min).

Overall, even under varying experimental conditions, the average FiO_2 differed significantly among the 4 oxygen injection sites (all $P < 0.0001$). Moreover, the highest average FiO_2 was consistently found when oxygen was injected at the mask, expect for

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only one experimental condition (Figure 3D, single arched valve, 25/10 cmH_2O, and oxygen flow rate of 5 L/min).

Table 1 summarizes the effects of these different factors on FiO_2 during simulated NPPV. After adjusting for the other factors, the mean FiO_2 values were significantly increased for a higher oxygen flow rate (10 L/min vs. 5 L/min, increased 48.5%, adjusted mean difference = 11.05, 95% CI = 10.28 to 11.81; $P < 0.0001$), a lower inspiratory pressure (15 cmH_2O vs. 25 cmH_2O, increased 13.3%, adjusted mean difference = 3.03, 95% CI = 2.27 to 3.79; $P < 0.0001$) and a lower expiratory pressure (5 cmH_2O vs. 10 cmH_2O, increased 11.3%, adjusted mean difference = 2.57, 95% CI = 1.81 to 3.33; $P < 0.0001$), the use of a single-arch valve (compared to mask valve, increased 9.6%, adjusted mean difference = 2.19, 95% CI = 1.26 to 3.13; $P < 0.0001$), and when the oxygen injection site was at the mask (compared to proximal to ventilator, increased 70.2%, adjusted mean difference = 15.99, 95% CI = 14.91 to 17.07; $P < 0.0001$).

Based on comparisons by F-tests using type III sums of squares, all five of these experimental factors had significant effects on FiO_2 after adjusting for other experimental factors (All $P < 0.0001$). Moreover, among these 5 factors, the oxygen injection site had the greatest effect on FiO_2, which was followed by the oxygen flow rate, the type of exhalation valve, the inspiratory pressure, and the expiratory pressure.

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Discussion

Clinically, supplemental oxygen is often added to a NPPV circuit to maintain the blood saturation level at > 90% for patients with acute respiratory failure.[1] Multiple factors can affect the amount of oxygen that is inspired by a patient. In this study, we found that the oxygen injection site relative to the head model remarkably affected the concentration of inspired oxygen; for a given oxygen flow rate, the oxygen injection site had the greatest effect on the fraction of inspired oxygen (FiO_2). Additionally, an oxygen injection site that was closer to a patient resulted in a higher concentration of delivered oxygen. The highest delivered oxygen concentration was when oxygen was injected at the mask, and the lowest inspired oxygen concentration was when oxygen was added proximal to the ventilator. (The higher delivered oxygen concentration may have been due to a lack of oxygen leak through the exhalation port before inspired gas reached the mask.) A higher oxygen flow also increased the inspired oxygen concentration. The type of exhalation valve also affected the inspired oxygen concentration.

Waugh et al.[9] found the highest inspired oxygen concentration when oxygen was added into the circuit at the ventilator outlet; however, they only used a mask valve. Also, their in vitro model was passive analog lung NPPV, which cannot simulate spontaneous breathing, and it had pressure control ventilation, which is different from NPPV with pressure support ventilation. Schwartz et al. [8] found that the type of exhalation valve

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affected the delivered oxygen concentration; the inspired oxygen concentration was greater when oxygen was added proximal to the ventilator with the leak port located in the mask, or when oxygen was added to the mask and the leak port was in the respiratory circuit. However, Schwarz et al. used a mask valve that was different from ours and may have reduced the actual delivered FiO_2. Also, the oxygen sensor used for their oxygen measurements had a much slower response time (30 s) for a 90% change than ours (300 ms).

Thys et al.[7] also found that adding oxygen between the patient and the exhalation valve resulted in a lower delivered oxygen concentration than when adding oxygen between the exhalation valve and the ventilator. However, Thys et al. studied human subjects; thus, they could not determine when oxygen was added to the mask and the actual FiO_2 delivered to a patient. They also used a oxygen sensor with a slow response time. Yet, delivered oxygen concentration was higher at lower inspiratory (15 cmH_20) and expiratory (5 cmH_20) pressures[7-9] and at a higher oxygen flow rate.[7, 9] In practice, the oxygen injection site should be selected based on the clinical situation. For example, an oxygen tube can easily fall off if oxygen is injected into a mask, and a specialized adapter is needed when oxygen is added at a humidifier outlet.

In previous studies,[6-10] the response times of the oxygen sensors for which a 90% change was used to measure oxygen concentration were slow (12-43 sec) and they did not

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distinguish between the inspiratory phase and the expiratory phase. Inspired oxygen concentration is relatively low at the beginning of the inspiratory cycle while the inspiratory flow is high, whereas oxygen concentration is highest at the end while the inspiratory flow is lowest with less efficient oxygen delivery. We used an improved oxygen sensor with a 300 ms response time and software of our design that allowed us to more closely calculate the actual inspired oxygen concentration.

One difficulty with measuring the actual delivered oxygen concentration is rebreathing of exhaled gases such that inhaled and exhaled gases are mixed together. The standard portable bi-level positive airway pressure circuit is a one-way loop, which increases the likelihood of rebreathing.[11] To lessen this effect, we used a condition that had been previously shown to minimize rebreathing; a medium-sized mask with expiratory pressure set at 5 cmH_2O.[12] Even so, rebreathing could obviously affect the inspired oxygen concentration, which was one limitation of our study.

Our intent was not to predict precise oxygen concentrations for all parameters. Rather, we wanted to systematically test the general effects of these variables to estimate conditions that would be relevant for patients. That is, controllable NPPV circuit variables that can most affect oxygen delivery and may help us distinguish patients' increased oxygen needs due to their worsening conditions or due to other factors that affect fraction inspired oxygen (FiO_2). Although, noninvasive ventilators with oxygen blenders are not popular at least in China,

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many patients in the acute phases can only use alternatives to these noninvasive ventilators without oxygen blender, we should regard noninvasive ventilator with oxygen blender as first choice in those patients. Low-flow oxygen and pressures in the range of 20 cmH_20 are reasonably safe while for higher flows and high pressures the margin of error increases and this may occur in the acute phases where none had to use these ventilators in medical, surgical, emergency room units.

As shown in Figure 3, when all of our variables were included in general linear models, the most obvious effect was due to the oxygen injection site (for a given oxygen flow rate). In addition, our improved response time oxygen sensor and software should be readily applicable to other studies in which oxygen concentration varies rapidly. Additionally, for oxygen bottles or oxygen concentrators that are used as oxygen sources in family's homes , a user can preserve the oxygen source by selecting a suitable oxygen injection location. This is a very important application for family-use of non-invasive ventilation.

In conclusion, we found that the site of oxygen delivery into the ventilation circuit, the type of exhalation mask, the oxygen flow rate, and the inspiratory and expiratory pressures, affected the delivered fraction inspired oxygen). Among all the variables we examined, for a given oxygen flow rate, the oxygen injection site had the most significant effect on the inspired oxygen concentration during NPPV, which is a clinically controllable

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variable. Thus, this factor should be given more consideration during NPPV therapy.

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None

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FIGURE LEGENDS

Figure 1: Schematic diagram of the in vitro experimental apparatus.

Figure 2: Graph of an inhalation/exhalation curve (top) and the formula used for calculating oxygen concentration (bottom).

Figure 3: Comparisons of FiO_2 values with different experimental conditions.

FiO_2 values were determined for 4 injection port sites (see x-axes labels) and 2 oxygen flow rates (5 L/min, squares, and 10 L/min, circles) in a single arched valve at different inspiratory and expiratory pressures combinations: (A) 15/5 cmH_2O ; (B) 15/10 cmH_2O ; (C) 25/5 cmH_2O; and (D) 25/10 cmH_2O. Results are means and standard deviations (SD's); however, SD's were relatively small and difficult to display. $^{*}P$ <0.05 compared to ventilator proximal; $^{\dagger}P$ <0.05 compared to humidifier; $^{\ddagger}P$ <0.05 compared to in front of the exhalation valve.

Figure 4: Comparisons of FiO_2 values with different experimental conditions.

FiO_2 values were determined for 4 injection port sites (see x-axes labels) and 2 oxygen flow rates (5 L/min, squares, and 10 L/min, circles) in a plateau exhalation valve at different inspiratory and expiratory pressures combinations: (A) 15/5 cmH_2O ; (B) 15/10 cmH_2O ; (C) 25/5 cmH_2O; and (D) 25/10 cmH_2O. Results are means and standard deviations (SD's); however, SD's were relatively small and difficult to display. $^{*}P$ <0.05

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compared to ventilator proximal; $^{\dagger}P$ <0.05 compared to humidifier; ‡ P <0.05 compared to in front of the exhalation valve.

Figure 5: Comparisons of FiO_2 values with different experimental conditions.

FiO_2 values were determined for 4 injection port sites (see x-axes labels) and 2 oxygen flow rates (5 L/min, squares, and 10 L/min, circles) in a mask valve at different inspiratory and expiratory pressures combinations: (A) 15/5 cmH_2O ; (B) 15/10 cmH_2O ; (C) 25/5 cmH_2O; and (D) 25/10 cmH_2O. Results are means and standard deviations (SD's); however, SD's were relatively small and difficult to display. $^{*}P$ <0.05 compared to ventilator proximal; $^{\dagger}P$ <0.05 compared to humidifier; ‡ P <0.05 compared to in front of the exhalation valve.

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Table 1. Experimental factor effects on FiO_2 during simulated non-invasive positive pressure ventilation (NPPV) assessed using general linear models

Experimental factors	Adjusted mean difference[†]	95% CI	*P*-value
Oxygen flow[a]			
5 L/min	Referent group	--	--
10 L/min	11.05	(10.28, 11.81)	<0.0001
Inspiratory pressure[b]			
25 cmH_2O	Referent group	--	--
15 cmH_2O	3.03	(2.27, 3.79)	<0.0001
Expiratory pressure[c]			
10 cmH_2O	Referent group	--	--
5 cmH_2O	2.57	(1.81, 3.33)	<0.0001
Exhalation valve[d]			
Mask valve	Referent group	--	--
Plateau exhalation valve	-2.04	(-2.98, -1.11)	<0.0001
Single-arch valve	2.19	(1.26, 3.13)	<0.0001
Oxygen injections sites[e]			
Proximal to ventilator	Referent group	--	--
Humidifier outlet	9.10	(8.03, 10.18)	<0.0001
In front of exhalation valve	5.81	(4.73, 6.89)	<0.0001
Mask	15.99	(14.91, 17.07)	<0.0001

CI: confidence interval.

[†]Adjusted mean differences in FiO_2 compared to the referent group when controlled for other experimental factors.

F-tests using type III sums of squares:

[a]$F_{1, 279} = 813.49$, *P*-value = 1.11×10^{-84};

[b]$F_{1, 279} = 61.27$, *P*-value = 1.04×10^{-13};

[c]$F_{1, 279} = 44.11$, *P*-value = 1.62×10^{-10};

[d]$F_{2, 279} = 39.89$, *P*-value = 5.80×10^{-16};

[e]$F_{3, 279} = 296.88$; *P*-value = 1.72×10^{-86}.

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Figure 1

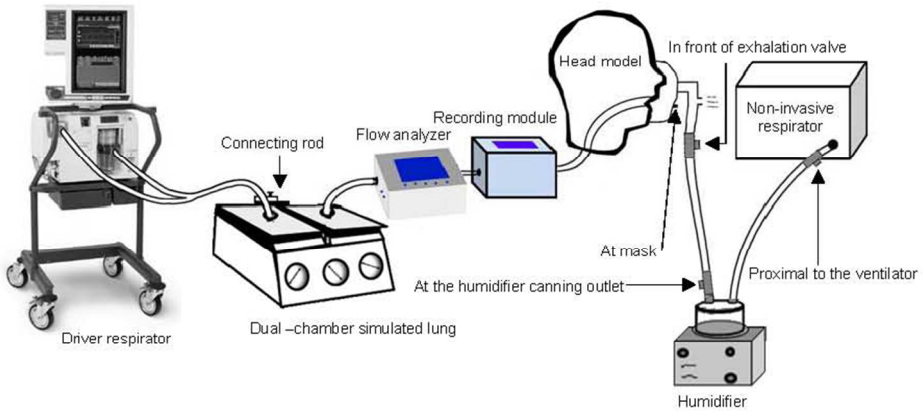

Figure 1
160x89mm (152 x 152 DPI)

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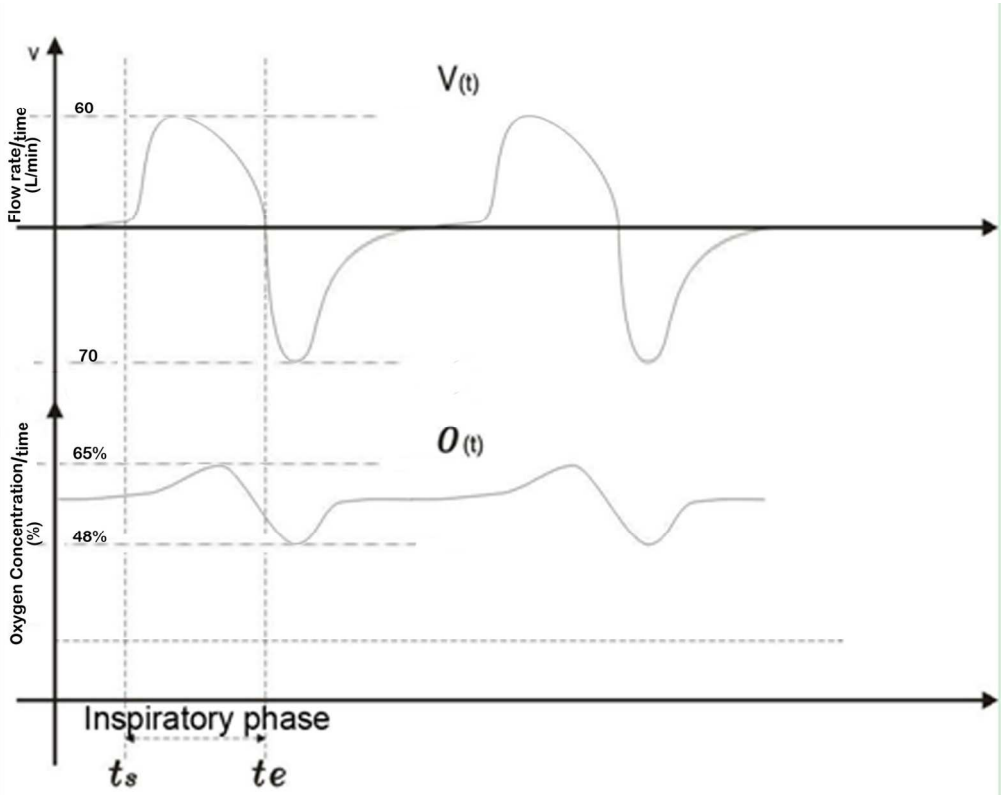

$$FiO_2 = \frac{V_{O2} = \int_{ts}^{te} V_{(t)} O_2\%_{(t)} d_{(t)}}{Vt = \int_{ts}^{te} V_{(t)} d_{(t)}} \times 100\%$$

Figure 2
73x85mm (600 x 600 DPI)

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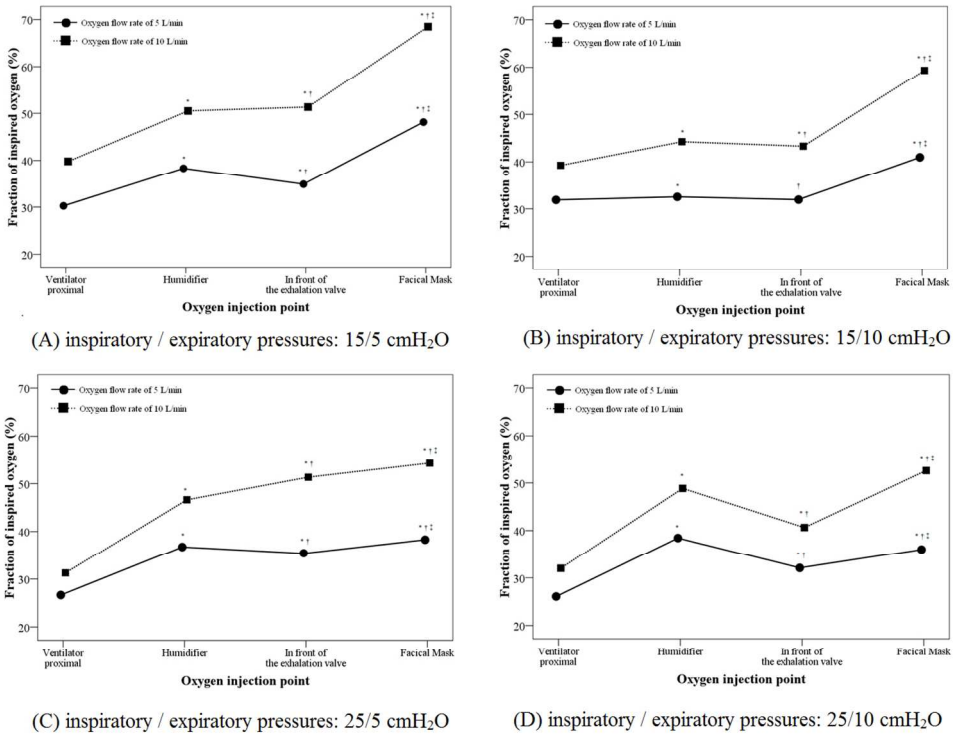

(A) inspiratory / expiratory pressures: 15/5 cmH_2O

(B) inspiratory / expiratory pressures: 15/10 cmH_2O

(C) inspiratory / expiratory pressures: 25/5 cmH_2O

(D) inspiratory / expiratory pressures: 25/10 cmH_2O

Figure 3
121x92mm (300 x 300 DPI)

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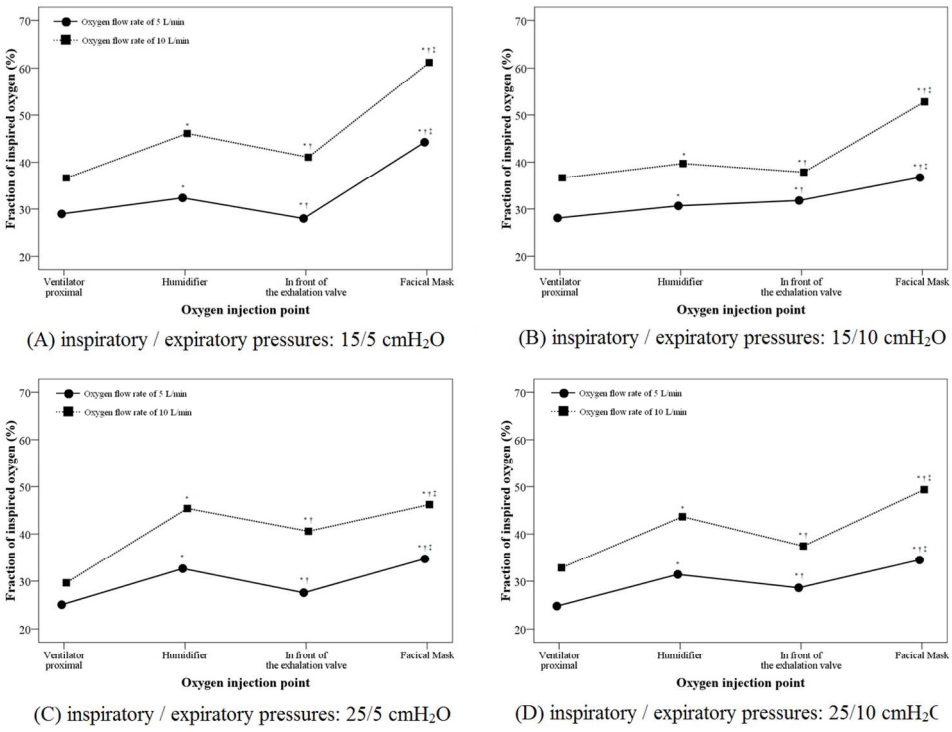

(A) inspiratory / expiratory pressures: 15/5 cmH_2O

(B) inspiratory / expiratory pressures: 15/10 cmH_2O

(C) inspiratory / expiratory pressures: 25/5 cmH_2O

(D) inspiratory / expiratory pressures: 25/10 cmH_2C

Figure 4
121x92mm (300 x 300 DPI)

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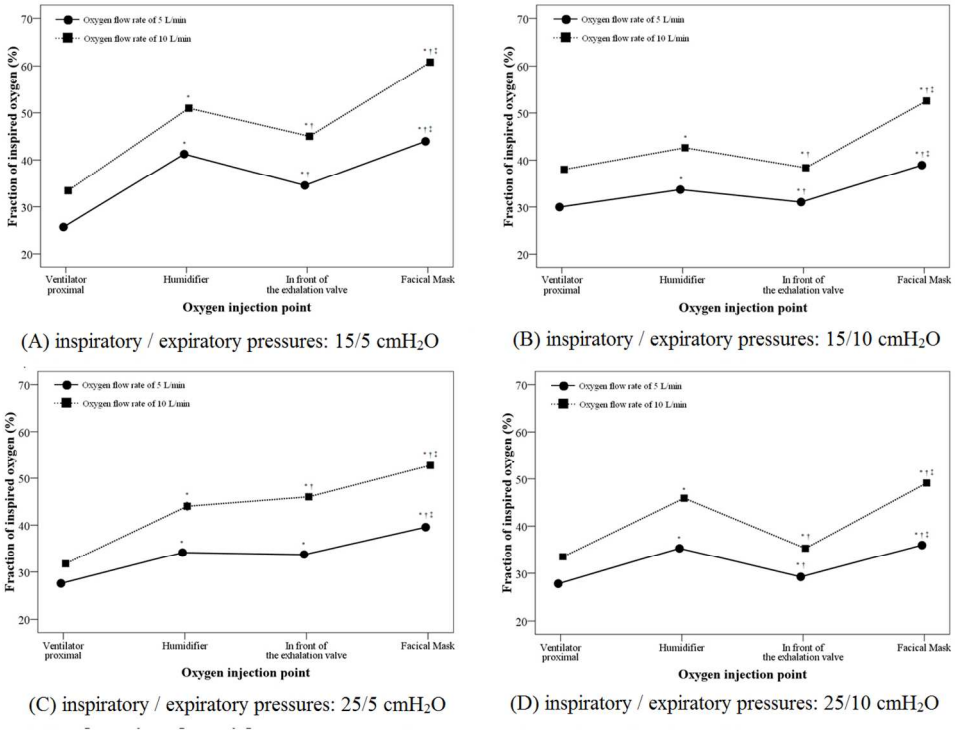

Figure 5
121x92mm (300 x 300 DPI)

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