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Breathing pattern in weaning patients: comparison of two inspired oxygen fractions

A influência de duas frações inspiradas de oxigênio no padrão respiratório de pacientes sob desmame ventilatório

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ABSTRACT

Background and objectives: An inspired oxygen fraction (FiO_2) of 40% is often used for weaning patients, but lower FiO_2 values are also recommended, if arterial oxygen pressure (PaO_2)/ FiO_2 ≥150–200 mmHg. This study aimed to compare respiratory variables and vital data values recorded during use of sufficient FiO_2 (ideal) to maintain peripheral oxygen saturation at 92% with values recorded during use of FiO_2 established at 40% (baseline) in weaning patients.

Methods: Prospective cross-over study. Respiratory variables (respiratory frequency, tidal volume, occlusion pressure, inspiratory time/total time ratio) and vital data (blood pressure and heart rate) were collected sequentially at 30 and 60 minutes with baseline FiO_2, followed by ideal FiO_2. These were compared to a generalized linear model for repeated measurements. Comparisons between baseline and ideal FiO_2 values, and arterial blood gases were evaluated by the Student's t or Wilcoxon tests.

Results: In 30 adult patients the median of ideal FiO_2 was 25% (IQ25%-75% 23-28). This was significantly lower than baseline FiO_2 (40%) (p< 0.001). No significant difference was found in the PaO_2/ FiO_2 ratio between baseline FiO_2 (269±53) and ideal FiO_2 (268±47). Tidal volume was significantly lower during use of ideal FiO_2 (p=0.003) and blood pressure was significantly higher during use of baseline FiO_2 (p=0.041), but there was no clinical significance. The remaining variables were not affected by reduction in FiO_2. The ideal FiO_2 did not influence remaining variables.

Conclusions: These results suggest that FiO_2 levels sufficient to ensure a SpO_2≥92% did not alter breathing patterns or trigger clinical changes in weaning patients.

Keywords: Respiration; Respiratory mechanics; Mechanical ventilation; Oxygen inhalation therapy; Ventilator weaning

INTRODUCTION

Supplemental inspired oxygen fraction (FiO_2) is a mechanical ventilation parameter often used to optimize tissue oxygenation. However, an inadequate adjustment of FiO_2 may lead to hypoxia or hyperoxia and, consequently, to noxious effects.(1-3) Several cellular alterations and an increased anaerobic metabolism are some of the consequences of tissue hypoxia.(4) When an individual is in a situation of acute hypoxemia, there may be an increased stimulus of peripheral chemoreceptors and therefore increase of respiratory drive, which is defined as the lowest central stimulus able to generate a motor response in the inspiratory muscles.(5) In patients under mechanical ventilation, respiratory drive is directly related to the patient and mechanical ventilator interaction.(6) The respiratory pattern is directly influenced by the drive and is regarded as a set of factors related to respiratory frequency and depth, such as flow, minute volume, inspiration and expiration times as well as associated variables such as the inspiratory time/total time ratio (Ti/Ttot).[7]

Toxic effects of oxygen are not well established in humans, but when administered in high doses or for a prolonged period, oxygen can cause pulmonary and systemic injuries.[8,9] In case of hyperoxia, the principal mechanism involved in these injuries is oxidative stress.[10,11] This can lead to degenerative processes of organic biomolecules, with subsequent cell failure and death.[12] Concerning pulmonary inflammation, activation and recruitment, of neutrophils and alveolar macrophages may occur , resulting in hyaline membrane formation, edema, hyperplasia and proliferation of type II alveolar epithelial cells, type I epithelial cells destruction, interstitial fibrosis and vascular pulmonary remodelling.[13]

To avoid harmful effects of hypoxia or hyperoxia on the organism, a FiO_2 higher than that of the surrounding air is recommended as adjuvant therapy when arterial oxygen pressure (PaO_2) is below 60 mmHg or $SaO_2 \leq 90\%$.[14] For weaning adult patients, criteria for assessment of mechanical ventilation discontinuation are adequate oxygenation (eg, PaO_2/FiO_2 ratio ≥ 150 to 200; requiring positive end-expiratory pressure [PEEP] ≤ 5 to 8 cmH_2O; $FiO_2 \leq 40$ to 50%).[15] Many patients undergoi prolonged mechanical ventilation[16,17] and consequently prolonged use of oxygen. These patients should receive a FiO_2 sufficient to meet their needs without changes in their breathing patterns and vital data. As such, , the aim of this study was to compare respiratory variables and vital data values recorded during use of FiO_2 at sufficient levels to maintain peripheral oxygen saturation (SpO_2) ≥ 92% with variables recorded during use of a baseline FiO_2 at 40% in stable patients being weaned from mechanical ventilation. The secondary objective was to determine the effect of exposure time on these variables of each FiO_2 level. The hypothesis was that such patients would exhibit no significant alterations in their respiratory variables and vital data values, because a SpO_2 level considered safe enough to avoid hypoxia in stable patients would be ensured.

METHODS

Study Patients

This was a prospective cross-over study that took place between April and December 2006, in one intensive care unit (ICU). The sample comprised 30 weaning patients, over 18 years of age, who had been on mechanical ventilation for more than 48 hours, due to different causes of respiratory failure. At the time of the study, all patients were on weaning from mechanical ventilation and on a 40% baseline FiO_2. Criteria used for considering patients as undergoing weaning from mechanical ventilation were those described in literature.[15]

Exclusion criteria were hemodynamic instability, severe cardiomyopathy or recent acute coronary syndrome. Patients with hemoglobin levels below 8 g/dL; those without adequate monitoring of SpO_2; with significant hydroelectrolytic, acid-base and metabolic disorders, neuromuscular diseases or need for sedation were also excluded. This study was approved by the Ethics Committee of the Governador Israel Pinheiro Hospital. Terms of informed consent were signed either by the patients or legal guardians.

Study Protocol

Respiratory pattern and drive variables were assessed from the mechanical ventilator monitor. The mechanical ventilator used was the Servoi® (Maquet Critical Care AB, Solna, Sweden). This model has an automatic calibration of FiO_2 and continuously monitors pressure in the first 100 milliseconds of an occluded inspiration ($P_{0.1}$) (used to estimate respiratory drive)[18] and the Ti/Ttot ratio (reflecting contraction duration of the inspiratory muscles).[7] Respiratory frequency (f), tidal volume (V_T) and Ti/Ttot ratio were recorded from a single measurement. $P_{0.1}$ was obtained from the average of three consecutive measurements. Patients on pressure support ventilation (PSV) were studied. Professionals who had no knowledge about this study defined all ventilatory parameters in accordance with each patient‘s clinical conditions.

Heart rate (HR), mean arterial pressure (MAP) and SpO_2 were monitored using Dixtal heart and oximetric monitors (DX 2010®, Dixtal Biomédica, São Paulo) and values were recorded throughout all phases of the study. The sampled arterial blood was analyzed periodically using a calibrated ABL 520 gasometer (Radiometer®, Copenhagen, Denmark). Complementary data was obtained from each patient at the time of collection.

Aspiration of pulmonary secretions was performed 30 minutes prior to data collection. Each patient was then placed in supine position with the headrest at 45 degrees. The variables of interest were then collected in two phases, each lasting one hour. The first phase was denominated baseline FiO_2 and was carried out with the patient on 40% FiO_2. The second was denominated ideal FiO_2 because it used an acceptable SpO_2 for stable patients,[14] in which SpO_2 was adjusted to a level sufficient to maintain it at 92% for Caucasians and 95% for Black individuals.[19] Ideal FiO_2 was determined after completion of the first phase; the FiO_2 was adjusted to 25% for all patients and observed for ten minutes. According to Cakar et al.,[20] this is sufficient time for a balance of the PaO_2 and SpO_2 following FiO_2 alterations in stable patients. After 10 minutes, FiO_2 was readjusted only if the desired SpO_2 had not yet been achieved and the same stabilization period was maintained until the ideal FiO_2 was obtained. Once this FiO_2 was determined, the second phase of the study began.

Data collection of respiratory variables and vital data were made every 30 and 60 minutes after onset of each phase to determine a possible influence of time. Arterial blood sample for blood gas analysis and lactate measurement was collected only 30 minutes after onset of each phase, to minimize the discomfort of radial artery punction. Pressure support and positive end-expiratory pressure (PEEP) remained unchanged throughout the study period. In accordance with the routine protocol of the service, FiO_2 of each patient was readjusted to 40% after completion of the second stage.

Statistical analysis

Data were analyzed using the SPSS 11.5 (SPSS Inc. Chicago, Illinois) and Prism 3 (GraphPad Software, San Diego) software programs. The information collected was presented either in absolute values, median (IQ25%-75%) or as the mean ± SD.

Respiratory variables and vital data were analyzed using the generalized linear model for repeated measurements with the Wilk's Lambda test, which investigated two effects: FiO_2 (baseline and ideal) and time (30 and 60 minutes). According to the test for normality, the paired Student's *t* test or the Wilcoxon test were used to compare PaO_2, arterial carbon dioxide pressure ($PaCO_2$), pH, arterial oxygen saturation (SaO_2), lactate, SpO_2, ideal FiO_2 in relation to baseline FiO_2, and the PaO_2/ FiO_2 ratio between the two study phases (use of different FiO_2 values). A two-sided p-value < 0.05 was considered significant.

RESULTS

All the 30 patients initially recruited completed the protocol. Of these 21 were male, mean age was 61±14 years and main reasons for mechanical ventilation were: pneumonia, complications after abdominal surgery, sepsis and stroke. Their demographic and clinical characteristics are shown in table 1. The median of ideal FiO_2 was 25% (IQ25%-75% 23-28). This result was significantly lower than baseline FiO_2 (40%) ($p<0.001$). PaO_2, SaO_2 and SpO_2 were significantly lower at 30 minutes during use of ideal FiO_2 ($p<0.001$, $p<0.001$, $p<0.001$, respectively), whereas no significant difference was observed regarding $PaCO_2$ ($p=0.21$) (Table 2). Lactate (1.42±0.56 and 1.41±0.52 mmol/L) and PaO_2/ FiO_2 (268±47 and 269±53) values obtained from ideal FiO_2 and baseline ideal, respectively, were not significantly different between the two phases. Among all patients studied, four (13%) had a PaO_2 < 60 mmHg during use of ideal FiO_2. Table 3 shows the PaO_2, SaO_2, SpO_2, *f* and HR values during the two study phases.

Respiratory variables and vital data assessed throughout the study time using different FiO_2 values are shown in table 4. Tidal volume (V_T) was significantly lower at 30 minutes during use of ideal FiO_2

Table 1- Patient clinical features

Variable	Result
N	30
Mean age (years)	61 ± 14
Gender	
Male	21
Female	9
Skin color	
White	26
Black	4
Weight (Kg)	74 ± 9
Hemoglobin (g/dL)	9.2 ± 1.2
APACHE II	14 (9,5-20)
Artificial airway	
Tracheostomy cannula	18
Oro-tracheal tube	12
Reason for use of MV	
Pneumonia	7
Complications after abdominal surgery	7
Sepsis	5
Stroke	4
Other	7
Duration of MV at time of study (days)	12 ± 6
Baseline MV parameters	
Pressure support, cmH_2O	10 ± 3
PEEP, cmH_2O	6 ± 1

APACHE II - Acute Physiology and Chronic Health Disease Classification System II; PEEP - positive end-expiratory pressure; MV- mechanical ventilation. Results are presented in absolute values; median (IQ 25%-75%); mean ± SD.

in comparison to that at 30 and 60 minutes after onset of baseline FiO_2, and no significant difference was observed in intragroup analyses. When considering interaction between the two FiO_2 levels used and the two patient exposure times for each FiO_2, a significant difference was observed only in the MAP variable. It was significantly higher during the first 30 minutes of the baseline FiO_2 phase then at other times of exposure. The remaining variables demonstrated no significant alterations with regard to different FiO_2 levels or exposure times.

Table 2 – Gas exchange parameters observed during the use of baseline FiO_2 and ideal FiO_2

	Baseline FiO_2	Ideal FiO_2	P value
FiO_2 (%)	40.0	24.9 ± 2.5 25 (21-30)	<0. 001*
PaO_2 (mmHg)	107.4 ± 21.2	65.6 ± 7.8	<0.001*
$PaCO_2$ (mmHg)	36.2 ± 6.8	34.7 ± 6.4	0.21
SaO_2 (%)	97.8 ± 1.2	92.5 ± 2.4	<0.001*
SpO_2 (%)	97.7 ± 0.9 98 (97-98)	92.7 ± 1.34 92 (92-93)	<0.001*

FiO_2 - inspired oxygen fraction; PaO_2 - Arterial Oxygen Pressure; $PaCO_2$ - Arterial Carbon Dioxide Pressure; SaO_2 - Arterial Oxygen Saturation and SpO_2 - Peripheral Oxygen Saturation. Results are presented in median (IQ 25%-75%) or mean ± SD. *$p < 0.05$ compared with baseline FiO_2

DISCUSSION

The main finding of the present study was that reduction of 40% FiO_2 to a level sufficient to assure $SpO_2 \geq 92\%$ did not alter the breathing pattern and/or trigger clinical changes in stable patients undergoing weaning from mechanical ventilation. However, there was a significant difference between baseline FiO_2 and tideal FiO_2 values for each patient. The clinical implication of these findings is that it is possible to reduce FiO_2 without affecting the PaO_2 / FiO_2, ensuring gas exchange.

No significant alterations in variables related to the respiratory pattern and drive were observed in this study, except for a reduction in V_T 30 minutes after onset of the ideal FiO_2 phase. However, this finding does not seem to have clinical significance, as the V_T value considered ideal during weaning from mechanical ventilation ranges from 4 to 6 mL/kg of ideal weight. One reason for reduction in V_T is the inhibition of chemoreceptors through reduction of $PaCO_2$. In our study, no significant variation was observed in $PaCO_2$ levels during the different FiO_2 regimens used. This may be due to the fact that patient respiratory patterns did not change. Values of average lactate and Ti/Ttot ratio remained within ranges considered nor-

Table 3 – Comparison of gas exchange parameters and vital data of the four patients with hypoxemia during the use of ideal FiO_2

	PaO_2 (mmHg)		SaO_2 (%)		SpO_2 (%)		f (irpm)		HR (bpm)	
Patient	Baseline FiO_2	Ideal FiO_2	Baseline FiO_2	Ideal iO_2	Baseline FiO_2	Ideal FiO_2	Baseline FiO_2	Ideal FiO_2	Baseline FiO_2	Ideal FiO_2
1	86.9	52.8	97.1	88.2	97	92	24	26	80	84
2	85.3	57.4	96.7	89	97	92	24	25	91	93
3	82.1	52.5	96.4	87.7	96	92	18	23	85	92
4	88.4	56.1	97.2	88.8	97	92	24	25	88	96

FiO_2 – inspired oxygen fraction; PaO_2 - arterial oxygen pressure; SaO_2 - arterial oxygen saturation; SpO_2 - peripheral oxygen saturation;
f - respiratory frequency; HR – heart rate

Table 4 - Respiratory variables and vital data observed during the use of baseline and ideal inspired oxygen fraction

FiO_2	Time	*f* (irpm)	V_T (mL/Kg)	Ti/Ttot (s)	$P_{0.1}$ (cmH_2O)	HR (bpm)	MAP (mmHg)
Baseline	30 minutes	22.0 ± 4.3	6.35 ± 0.11	0.30± 0.06	1.6 ± 0.8	100.0 ± 19.1	109.8 ± 15.0**
	60 minutes	22.8 ± 4.1	6.48 ± 0.12	0.30± 0.06	1.5 ± 0.8	100.0 ± 17.3	105.9 ± 13.9
Ideal	30 minutes	22.9 ± 4.5	5.94 ± 0.10*	0.29± 0.06	1.6 ± 1.2	101.7 ± 16.2	106.5 ± 17.4
	60 minutes	22.7 ± 4.8	6.08 ± 0.08	0.31± 0.06	1.5 ± 1.0	99.7 ± 17.9	106.8 ± 16.9

FiO_2 – inspired oxygen fraction; *f* - respiratory frequency; V_T - tidal volume; Ti/Ttot - inspiratory time/total respiratory time ratio; $P_{0.1}$ - occlusion pressure; HR - heart rate; MAP - mean arterial blood pressure. Results are presented as average ± SD. * $p = 0.003$ compared with baseline FiO_2; ** $p = 0.041$ considering the interaction between FiO_2 and exposure time because was investigated two effects: FiO_2 (baseline and ideal) and time (30 and 60 minutes).

mal with both FiO_2 levels and no significant differences between them was found.

Unlike our results, Volta et al.[21] found that respiratory pattern and drive were modulated by variations in FiO_2. The authors observed that reduction of FiO_2 was associated to a significant increase of V_T, *f*, $P_{0.1}$ and dyspnea. However, differences of the ventilatory parameters used may explain the divergence from our results. Volta et al. compared predetermined FiO_2 levels (21 and 30%) to the 40% FiO_2 and found a significant difference only when FiO_2 was decreased from 40 to 30%. The pressure support level used for similar V_T in the two studies was also greater in the population of the Volta et al. study. This suggests that our patients were most likely at a greater mechanical advantage, which may have reflected positively on our results. In patients under adequate pressure support level, there is less overload on respiratory muscles, which translates to lower $P_{0.1}$ values.[22] Differences in methods of measuring time applied to the variables may also have favored divergences between results. Pesenti et al.[23] found an increased hypoxic respiratory drive after 20 minutes, even when SpO_2 was maintained at values considered adequate (90 to 95%). However, differences between the populations studied are also evident, especially because our patients were not under the effect of sedatives. The diagnostic heterogeneity of our population provides a greater clinical applicability of results. Furthermore, our patients were studied for a longer time than those of the studies cited, which may also have influenced findings.

Sensitivity to increase or decrease of oxygen level occurs through specialized chemoreceptor cells that regulate respiratory and cardiovascular response. This takes place acutely through activation of pre-existing proteins and chronically by regulation of genetic transcription.[24] However, hypoxic stimulation in the carotid body, only occurs where there is an important reduction in arterial oxygen content or when PaO_2 is lower than 60 mmHg. This stimulates neurosecretion by the glomic cells and causes the sensation of dyspnea.[25] Although dyspnea was not objectively assessed in this study, there was no report of respiratory discomfort by patients and, upon inspection, no accessory muscle action was observed.

No significant HR alterations were observed in this study. Thomson et al.[26] found an increased HR when assessing the effect of hypoxemia on the cardiovascular function of healthy volunteers. However, these individuals were exposed to 80 percent SpO_2, which is different from that in our population. Regarding MAP, a significantly higher value was observed in the first 30 minutes of the study. This may have occurred because patients were alert and possibly anxious in relation to the initial procedures of the study.

Absence of clinical and breathing pattern changes in our results may be explained by two main reasons. The first is that, at the time of the study, our patients no longer exhibited signs or symptoms of acute respiratory failure as demonstrated by a close to normal PaO_2/ FiO_2 . Despite this clinical condition, all patients were using a 40% baseline FiO_2. Moreover, average PaO_2 was higher than 65 mmHg in the population studied. Four patients had a PaO_2 of less than 60 mmHg, which probably occurred due to the 2 to 4% variability presented by most pulse oximeters. Adjustment of FiO_2 to an "ideal" value in this study was based on SpO_2, however, blood gas analyses were used only for control of blood gas data. For that, purpose FiO_2 was set at a value that would ensure a SpO_2 of 92%. Oximeter variability may have caused an improper adjustment of FiO_2 in these patients and therefore a PaO_2 of less than 60 mmHg. Respiratory frequency and heart rate increased in these four patients, probably in response to hypoxemia. The ideal FiO_2 should be higher than the adjusted, therefore risk of hypoxemia in these patients could be avoided if the SpO_2 cut-off point were raised to 94%.[27,28]

There are some limitations in our study**:** (1) lack of a control group, (2) non-randomization of the patients studied and (3) non-assessment of the clinical outcome of these patients. According to Benchetrit,[7] choice of control individuals is difficult in studies that involve ventilatory alterations due to the considerable variability regarding the diverse components of the respiratory pattern. In order to minimize this bias, each individual served as his own control. Assessment of the clinical outcome of weaning patients submitted to different FiO_2 levels could provide relevant information on oxygen use in this population. The total time of each patient on mechanical ventilation after data collection was not assessed, since this was not an objective of the present study.

CONCLUSION

This study suggests that FiO_2 levels sufficient to ensure a $SpO_2 \geq 92\%$ did not alter breathing patterns or trigger clinical changes in stable adult patients undergoing weaning from mechanical ventilation.

RESUMO

Introdução e objetivos: Frações inspiradas de oxigênio (FiO_2) ≤ 40% são recomendadas durante o desmame ventilatório se pressão arterial de oxigênio (PaO_2)/FiO_2 ≥150–200 mmHg, O objetivo desse estudo foi comparar as variáveis respiratórias e os dados vitais coletados durante a utilização de uma FiO_2 suficiente para manter a saturação periférica de oxigênio em 92% (ideal) com aquelas coletadas durante uma FiO_2 rotineiramente ajustada em 40% (basal) em pacientes sob desmame ventilatório.

Métodos*:* Estudo prospectivo cruzado. As variáveis freqüência respiratória, volume corrente, pressão de oclusão, relação tempo inspiratório/tempo total, pressão arterial e freqüência cardíaca foram coletados, seqüencialmente, aos 30 e 60 minutos sob FiO_2 basal (40%) e, em seguida sob FiO_2 ideal. Essas foram comparadas pelo modelo linear generalizado para medidas repetidas. Para comparar os valores basal e ideal da FiO_2 e da PaO_2 foram utilizados os testes *t* Student ou Wilcoxon.

Resultados: Em 30 pacientes adultos a mediana da FiO_2 ideal foi 25% (IQ25%-75% 23-28), significativamente menor que a basal (40%) (p< 0,001). A relação PaO_2/FiO_2 não apresentou diferença significativa entre a FiO_2 basal (269±53) e a FiO_2 ideal (268±47). O volume corrente foi significativamente menor durante a utilização da FiO_2 ideal (p=0,003) e a pressão arterial foi significativamente maior durante a utilização da FiO_2 ideal (p=0,041), mas sem significância clínica. A FiO_2 ideal não influenciou as demais variáveis.

Conclusão: Esses resultados sugerem que níveis de FiO_2 suficientes para manter uma SpO_2≥92% não alteraram o padrão respiratório ou provocaram alterações clínicas em pacientes sob desmame ventilatório.

Descritores: Respiração; Mecânica respiratória; Ventilação mecânica; Oxigenoterapia; Desmame do respirador

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