Role of Respiratory Drive in Hyperoxia-Induced Hypercapnia in Ready-to-Wean Subjects With COPD

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BACKGROUND: Hyperoxia-induced hypercapnia in subjects with COPD is mainly explained by alterations in the ventilation/perfusion ratio. However, it is unclear why respiratory drive does not prevent CO_2 retention. Some authors have highlighted the importance of respiratory drive in CO_2 increases during hyperoxia. The aim of the study was to examine the effects of hyperoxia on respiratory drive in subjects with COPD. METHODS: Fourteen intubated, ready-to-wean subjects with COPD were studied during normoxia and hyperoxia. A CO_2 response test was then performed with the rebreathing method to measure the hypercapnic drive response, defined as the ratio of change in airway-occlusion pressure 0.1 s after the start of inspiratory flow ($\Delta P_{0.1}$) to change in P_{aCO_2} (ΔP_{aCO_2}), and the hypercapnic ventilatory response, defined as the ratio of change in minute volume ($\Delta \dot{V}_E$) to ΔP_{aCO_2}. RESULTS: Hyperoxia produced a significant increase in P_{aCO_2} (55 ± 9 vs 58 ± 10 mm Hg, $P = .02$) and a decrease in pH (7.41 ± 0.05 vs 7.38 ± 0.05, $P = .01$) compared with normoxia, with a non-significant decrease in $\dot{V}_E$ (9.9 ± 2.9 vs 9.1 ± 2.3 L/min, $P = .16$) and no changes in $P_{0.1}$ (2.85 ± 1.40 vs 2.82 ± 1.16 cm H_2O, $P = .97$) The correlation between hyperoxia-induced changes in $\dot{V}_E$ and P_{aCO_2} was $r^2 = 0.38$ ($P = .02$). Median $\Delta P_{0.1}/\Delta P_{aCO_2}$ and $\Delta \dot{V}_E/\Delta P_{aCO_2}$ did not show significant differences between normoxia and hyperoxia: 0.22 (0.12–0.49) cm H_2O/mm Hg versus 0.25 (0.14–0.34) cm H_2O/mm Hg ($P = .30$) and 0.37 (0.12–0.54) L/min/mm Hg versus 0.35 (0.12–0.96) L/min/mm Hg ($P = .20$), respectively. CONCLUSIONS: In ready-to-wean subjects with COPD exacerbations, hyperoxia is followed by an increase in P_{aCO_2}, but it does not significantly modify the respiratory drive or the ventilatory response to hypercapnia.
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Introduction

Breathing high concentrations of oxygen may result in hypercapnia in subjects with COPD. Historically, the increased P_{aCO_2} resulting from oxygen administration in subjects with COPD was attributed to the oxygen-induced suppression of the hypoxic drive to breathe, with a consequent decrease in minute volume ($\dot{V}_E$). However, no strong data support this hypothesis.[1,2]

From 1980 onward, several studies investigated the mechanisms by which hyperoxia induces hypercapnia in subjects with COPD.[3-10] Most of these studies were conducted in non-intubated subjects with COPD through a mouthpiece, either in stable[5,8] or unstable[3,4,6] respiratory conditions. Most concluded that the control of ventilation played a minor role and suggested that the main mechanism to impair gas exchange during hyperoxia was a release of hypoxic pulmonary vasoconstriction that induced changes in the ventilation-perfusion distribution and entailed an increase in the dead-space-to-tidal-volume (V_T) ratio. However, it was uncertain why the respiratory drive did not prevent this CO_2 retention by increasing $\dot{V}_E$.

Although demonstrating an increase in dead space with hyperoxia in intubated subjects with COPD, Dunn et al[7]

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The authors has disclosed no conflicts of interest.

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identified alteration of respiratory drive during hyperoxia as an important mechanism in the pathogenesis of hypercapnia in subjects with COPD. Moreover, again with intubated, ready-to-wean subjects utilizing pressure support ventilation (PSV), Crossley et al[11] found no differences in P_{aCO_2} after hyperoxia in CO_2-retaining subjects with COPD. Robinson et al[6] studied ventilation-perfusion distribution in non-intubated subjects with COPD; they observed different responses to hyperoxia (some subjects experienced hypercapnia and others did not) and attributed hypercapnia to a reduction of overall ventilation rather than a redistribution of blood flow.

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In clinical practice, during the weaning period from mechanical ventilation, normoxia is the standard target in subjects with COPD. In this context and compared with hypoxia, the contribution of the release of hypoxic pulmonary vasoconstriction to the development of hyperoxia-induced hypercapnia should be reduced, and the role of respiratory drive could become more important.

Respiratory drive may be assessed through the negative pressure generated 100 ms after the onset of an occluded inspiration ($P_{0.1}$). $P_{0.1}$ is widely accepted as an index of respiratory drive performance,[12] although it may be affected by drugs, gas exchange, respiratory muscle function,[13] or lung volume. It is important to note that variations in P_{aCO_2} observed with hyperoxia in subjects with COPD may be not wide enough to produce a measurable change in $P_{0.1}$.[5,7,11] A CO_2 response test, which increases P_{aCO_2} by $>$ 10 mm Hg, may thus be a reliable method to compare the respiratory drive performance in normoxia and hyperoxia. However, there is an inherent variability in the measurement of the CO_2 response test[14,15] that can mislead the interpretation of small differences between normoxia and hyperoxia.

The aim of this investigation was to assess the influence of the central respiratory drive on the hyperoxia-induced hypercapnia that occurs in normoxic, intubated, ready-to-wean subjects with COPD. For this purpose, we compared respiratory physiologic parameters, including the results of the CO_2 response test, in normoxia and hyperoxia. Previously and according to the described variability of these measurements, we performed a reproducibility analysis of the CO_2 response.

QUICK LOOK

Current knowledge

Hyperoxia-induced hypercapnia in patients with COPD is attributed to alterations in ventilation/perfusion ratio, not an alteration in respiratory drive. However, it is unclear why respiratory drive does not prevent carbon dioxide retention.

What this paper contributes to our knowledge

In normoxic subjects with COPD requiring mechanical ventilation, at the time of weaning, hyperoxia does not seem to modify the central respiratory drive or the ventilatory response to hypercapnia. Hyperoxia is followed by a slight increase in P_{aCO_2}, possibly due to alterations in ventilation/perfusion matching and the Haldane effect.

Methods

Subjects

To analyze the reproducibility of the CO_2 response test, we prospectively studied 30 subjects connected to mechanical ventilation and ready to wean. To study the effects of hyperoxia, we prospectively studied 14 intubated subjects with COPD exacerbations who were recovering from acute respiratory failure and who fulfilled clinical criteria for a spontaneous breathing test.[16] All subjects were free of sedatives, awake, and able to obey commands. Informed consent was obtained from subjects or their closest relatives. The study had the approval of the institutional review board.

Study Protocol

Electrocardiogram, heart rate, pulse oximetry, invasive systemic blood pressure, and capnography (Capnostat CO_2 sensor, Marquette, Milwaukee, Wisconsin) were continuously monitored during the study. Pulmonary function measurements were carried out with the subject in a semi-recumbent position and after endotracheal suctioning.

All subjects were studied twice by the same investigator. For the reproducibility analysis, we performed the 2 repeated studies with an F_{IO_2} of 1. For the hyperoxia analysis, we performed the studies in normoxia and hyperoxia, with a crossover design in a random order. Normoxia was achieved by adjusting the F_{IO_2} to reach an S_{pO_2} of 89–94%. Hyperoxia was established with an F_{IO_2} of 1 for all subjects.

CO_2 Response Test

We followed the same methodology to perform the CO_2 response test in both the reproducibility and COPD groups of subjects. The CO_2 response test consisted of 2 sets of repeated measurements, first at baseline and then after reaching hypercapnia. Each CO_2 test lasted ~30 min.

Thirty min before the start of measurements, we adjusted the F_{IO_2} as defined by the study protocol. Fifteen min later, we set PSV mode with a pressure support of 7 cm H_2O and no PEEP. At the start of the measurements, $\dot{V}_E$, breathing frequency, and $P_{0.1}$ were recorded from the ventilator display (Evita 2 Dura or Evita 4, Dräger, Lübeck, Germany), and an arterial blood sample was drawn. While maintaining the subject breathing with PSV of 7 cm H_2O, we used the method of re-inhalation of expired air to reach hypercapnia[17-19] by inserting a corrugated tube between the Y-piece and the endotracheal tube, which increased the dead space,[17,18] by a volume similar to the V_T obtained with a pressure support of 7 cm H_2O. After at least 4 min of rebreathing and until exhaled CO_2 had increased by almost 10 mm Hg and remained constant, we again measured $\dot{V}_E$, breathing frequency, and $P_{0.1}$ and took another arterial blood sample. Once the CO_2 response test was finished, the added dead space was removed, and the subject was returned to the original ventilatory settings. A second CO_2 response test was repeated by the same investigator 1 h after finishing the first study with the F_{IO_2} adjusted according to the study protocol.

Measurements and Procedures

$P_{0.1}$ values were measured with the ventilator's built-in system,[20] and $P_{0.1}$ was calculated as the mean of 5 measurements at each point of the study.[21] Arterial blood gases were measured with a blood gas analyzer (IL-1650, Instrument Laboratory, Izasa, Spain).

We studied the following derived indexes: $\Delta\dot{V}_E/\Delta P_{aCO_2}$, which reflected the ventilatory response to hypercapnia and was calculated as the ratio of change in $\dot{V}_E$ to change in P_{aCO_2}; and $\Delta P_{0.1}/\Delta P_{aCO_2}$, which reflected the central drive response to hypercapnia and was calculated as the ratio of change in $P_{0.1}$ to change in P_{aCO_2}. The changes in $\dot{V}_E$, $P_{0.1}$, and P_{aCO_2} were determined as the difference between the value at the end of the hypercapnia test and the baseline value.

Statistical Analysis

To analyze the reproducibility of the CO_2 response test, we calculated the intraclass correlation coefficient (ICC) of consistency and agreement by analysis of variance. Differences in continuous variables between normoxia and hyperoxia were analyzed using the non-parametric Wilcoxon test for paired observations. Correlations between variables were explored using Pearson linear regression analysis. P values $< .05$ were considered significant. Continuous data were expressed as mean ± SD unless specified otherwise. Statistical analysis was performed with specific statistics software (SPSS 19.0, SPSS, Chicago, Illinois).

Table 1. Demographic and Clinical Characteristics of the 30 Subjects Included in the Reproducibility Analysis

Characteristic	Values
Age (mean ± SD), y	68 ± 10
Males, *n* (%)	17 (57)
Weight (mean ± SD), kg	73 ± 16
Height (mean ± SD), cm	164 ± 12
SAPS II score (mean ± SD)	41 ± 11
Duration of mechanical ventilation before study, d*	6 (2–5)

* Median (interquartile range)
SAPS II = Simplified Acute Physiology Score II

Results

Reproducibility Analysis of the CO_2 Response Test

Demographic and clinical characteristics of the 30 subjects included in this analysis are provided in Table 1. The reproducibility test for $\Delta P_{0.1}/\Delta P_{aCO_2}$ showed an ICC of consistency of 0.73 (95% CI 0.51–0.86) and an ICC of agreement of 0.76 (95% CI 0.51–0.87), showing a good correlation between the 2 measurements, with a bias between measurements of 0.015 cm H_2O/mm Hg ($P = .69$). For $\Delta\dot{V}_E/\Delta P_{aCO_2}$, the reliability test showed an ICC of consistency of 0.87 (95% CI 0.74 – 0.94) and an ICC of agreement of 0.86 (95% CI 0.72–0.93), showing an excellent correlation between the 2 measurements, with a bias between measurements of 0.068 L/min/mm Hg ($P = .06$).

Effects of Hyperoxia

Fourteen subjects with COPD (12 men) were studied. Demographic and clinical characteristics are presented in Table 2.

Table 2. Demographic and Clinical Characteristics of 14 Subjects With COPD Who Were Included in the Analysis of the Effects of Hyperoxia

Characteristic	Values
Age (mean ± SD), y	65 ± 8
Weight (mean ± SD), kg	88 ± 27
Height (mean ± SD), cm	164 ± 8
SAPS II score (mean ± SD)	38 ± 11
FEV_1 (mean ± SD), % predicted*	40 ± 18
FEV_1/FVC (mean ± SD), % predicted*	58 ± 17
Duration of mechanical ventilation before study, d†	3 (2–4)

* Measurements available in 12 subjects.
† Median (interquartile range)
SAPS II = Simplified Acute Physiology Score II

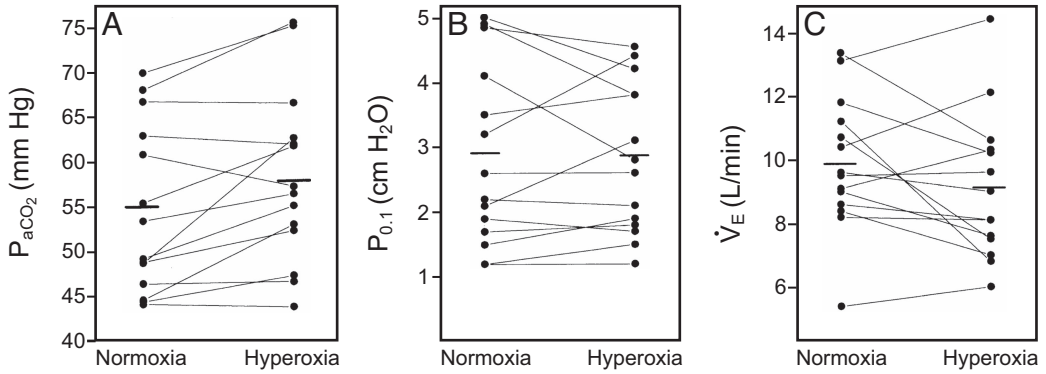

Fig. 1. Individual and mean (indicated by horizontal lines) baseline values of P_{aCO_2} ($P = .02$) (A), airway-occlusion pressure 0.1 s after the start of inspiratory flow ($P_{0.1}$; $P = .97$) (B), and minute volume ($\dot{V}_E$; $P = .10$) (C) in normoxia and hyperoxia.

Effect of Hyperoxia on Physiologic Variables

Hyperoxia induced a significant increase in P_{aCO_2}, P_{aO_2}, and mean blood pressure and a decrease in pH and heart rate compared with normoxia, together with a non-significant decrease in $\dot{V}_E$ and no changes in $P_{0.1}$ (Table 3). Individual baseline values of P_{aCO_2}, $P_{0.1}$, and $\dot{V}_E$ in normoxia and hyperoxia are shown in Figure 1.

Changes in $\dot{V}_E$ induced by hyperoxia showed a weak correlation with the increase in P_{aCO_2} induced by hyperoxia ($r^2 = 0.38$, $P = .02$) (Fig. 2), and no association was found between FEV_1 and changes in P_{aCO_2} induced by hyperoxia ($r^2 = 0.13$, $P = .24$).

Table 3. Baseline Physiologic Characteristics and CO_2 Response in Normoxia and Hyperoxia in 14 COPD Subjects

Characteristic	Normoxia	Hyperoxia	*P*
pH (mean ± SD)	7.41 ± 0.05	7.38 ± 0.05	.01
P_{aCO_2} (mean ± SD), mm Hg	55 ± 9	58 ± 10	.02
P_{aO_2} (mean ± SD), mm Hg	66 ± 4	359 ± 127	.001
$P_{0.1}$ (mean ± SD), cm H_2O	2.85 ± 1.40	2.82 ± 1.16	.97
$\dot{V}_E$ (mean ± SD), L/min	9.9 ± 2.9	9.1 ± 2.3	.16
Breathing frequency, breaths/min	24 ± 5	23 ± 5	.32
Mean blood pressure (mean ± SD), mm Hg	102 ± 16	107 ± 14	.04
Heart rate (mean ± SD), beats/min	89 ± 12	83 ± 11	.003
$\Delta P_{0.1}/\Delta P_{aCO_2}$, cm H_2O/mm Hg*	0.22 (0.12–0.49)	0.25 (0.14–0.34)	.30
$\Delta \dot{V}_E/\Delta P_{aCO_2}$, L/min/mm Hg*	0.37 (0.12–0.54)	0.35 (0.12–0.96)	.20

* Median (interquartile range)
$P_{0.1}$ = airway-occlusion pressure 0.1 s after the start of inspiratory flow
$\dot{V}_E$ = minute volume

Effects of Hyperoxia in CO_2 Response Test

The CO_2 response test in normoxia and hyperoxia did not show significant differences for both indexes studied ($\Delta \dot{V}_E/\Delta P_{aCO_2}$ and $\Delta P_{0.1}/\Delta P_{aCO_2}$) (see Table 3). Individual values are shown in Figure 3.

Changes in baseline P_{aCO_2} in normoxia and hyperoxia were not associated with changes in $\Delta P_{0.1}/\Delta P_{aCO_2}$ ($r^2 = 0.02$, $P = .6$) (Fig. 4A) and had a weak correlation with changes in $\Delta \dot{V}_E/\Delta P_{aCO_2}$ ($r^2 = 0.43$, $P = .01$) (Fig. 4B). According to COPD severity, $\Delta \dot{V}_E/\Delta P_{aCO_2}$ showed a positive correlation with FEV_1 ($r^2 = 0.61$, $P = .003$) that was not observed with $\Delta P_{0.1}/\Delta P_{aCO_2}$ ($r^2 = 0.03$, $P = .58$).

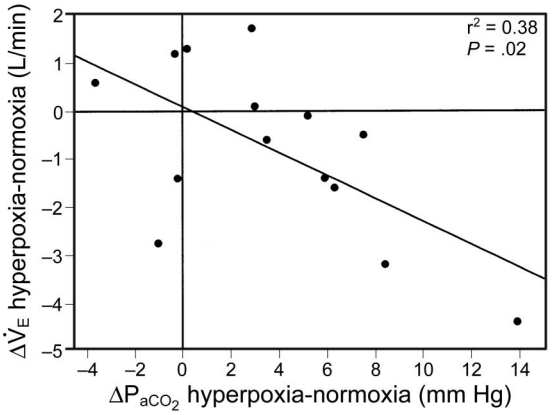

Fig. 2. Relationship between subject variations in P_{aCO_2} and minute volume ($\dot{V}_E$) induced by hyperoxia.

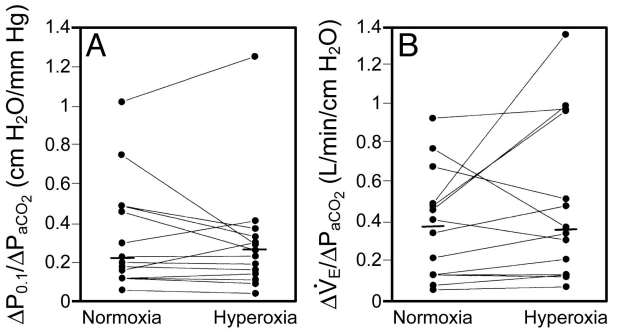

Fig. 3. Individual values and median of $\Delta P_{0.1}/\Delta P_{aCO_2}$ (where $P_{0.1}$ is airway-occlusion pressure 0.1 s after the start of inspiratory flow) (A) and $\Delta \dot{V}_E/\Delta P_{aCO_2}$ (where $\dot{V}_E$ is minute volume) (B) in normoxia and hyperoxia.

Discussion

We focused on assessing the role of central respiratory drive in oxygen-induced hypercapnia observed in subjects with COPD. According to our results, the small but significant increase in P_{aCO_2} induced by hyperoxia was not associated with a decrease in $P_{0.1}$. Indeed, mean baseline $P_{0.1}$ values were preserved and remained unaltered in our subjects. In accordance, although being reduced to some extent, $\Delta P_{0.1}/\Delta P_{aCO_2}$ in hyperoxia did not change significantly compared with normoxia, as found in other studies.[3,5,11] Our results suggest that an attenuation of respiratory drive functioning would not be the main mechanism to explain the hyperoxia-induced hypercapnia in normoxic, ready-to-wean subjects with COPD.

Nevertheless, there are some aspects that should be considered to carefully interpret these results. It should be noted that if the respiratory drive were intact, $\Delta P_{0.1}/\Delta P_{aCO_2}$ should have been increased compared with normoxia because of the rise in P_{aCO_2}. Therefore, a possible blunted response of the respiratory drive cannot be totally ruled out.

PSV could have decreased or increased the work of breathing and $P_{0.1}$ values depending on the amount of inspiratory assistance applied.[22] Several studies found no differences in work of breathing[23,24] or in $P_{0.1}$ measurements[24] during low levels of pressure support compared with T-piece breathing. In our study, if the level of pressure support applied had been low enough to entail an increase in $P_{0.1}$ due to the additional work of breathing caused by the endotracheal tube and the circuit, it could have counterbalanced an eventual decrease in $P_{0.1}$. Relative to $\dot{V}_E$, low levels of PSV may increase V_T compared with T-piece breathing.[23,24] However, as we applied the same ventilatory settings in normoxia and hyperoxia, it seems unlikely that this circumstance could significantly affect the comparison between the 2 conditions at baseline.

Hyperoxia induced in our subjects with COPD a nonsignificant decrease in $\dot{V}_E$ that was poorly correlated with changes in P_{aCO_2}. Other studies on subjects with COPD observed similar results.[4,5] The hyperoxia-induced hypercapnia observed in these studies was assumed to result principally from an increase in the dead-space-to-V_T ratio or from alterations in ventilation/perfusion matching rather than from a reduction in ventilation.[4,5] Because dead space is sensitive to changes in P_{aCO_2}, the Haldane effect on P_{aCO_2} might be responsible, in part, for the increase in dead space during hyperoxia.[25] Interestingly and in accordance with these results, Santos et al[10] observed an increase in P_{aCO_2} of 4 mm Hg while breathing 100% oxygen in 4 subjects with COPD connected to mechanical ventilation, sedated, and paralyzed, keeping $\dot{V}_E$ constant. The multiple inert gas elimination technique detected in these subjects an increase in the dispersion of blood flow distribution, suggesting a release of hypoxic pulmonary vasoconstriction as the main mechanism of hypercapnia. In

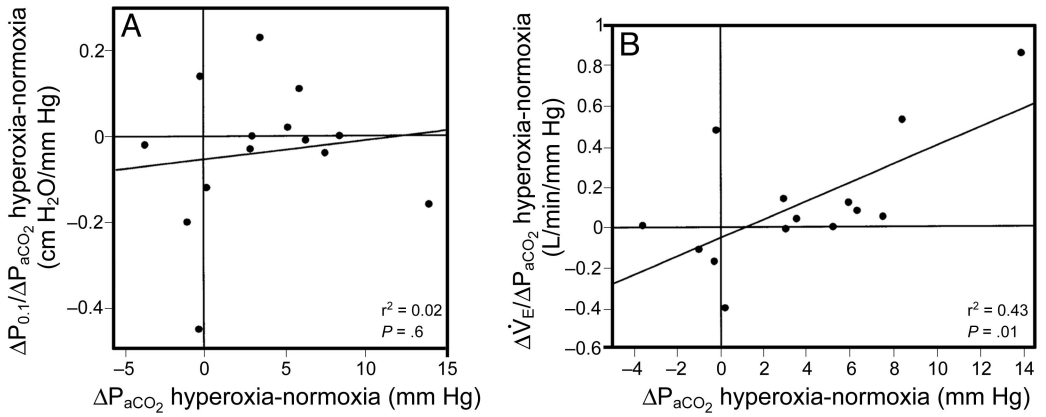

Fig. 4. Relationship between changes in baseline P_{aCO_2} induced by hyperoxia and the central drive response to hypercapnia ($\Delta P_{0.1}/\Delta P_{aCO_2}$, where $P_{0.1}$ is airway-occlusion pressure 0.1 s after the start of inspiratory flow) (A) and the ventilatory response to hypercapnia ($\Delta \dot{V}_E/\Delta P_{aCO_2}$, where $\dot{V}_E$ is minute volume) (B).

these experimental conditions of sedation and muscle relaxation, the influence of hyperoxia on the central respiratory drive response or the ventilatory response was totally abolished, and likewise, hypercapnia appeared.

Another feature that should be considered to explain the low correlation between the decrease in $\dot{V}_E$ and the increase in CO_2 is that the increase in CO_2 may be partially equilibrated by a concomitant decrease in CO_2 production. Certainly, there is a positive linear association between changes in CO_2 production and changes in $\dot{V}_E$.[4,5] The decrease in $\dot{V}_E$ may entail a decrease in the work of breathing and, as a result, a decrease in oxygen consumption and CO_2 production.[5] This phenomenon could also explain why 5 of our 14 subjects showed unexpected changes in P_{aCO_2} according to their changes in $\dot{V}_E$ (see Fig. 2). Unfortunately, we did not measure CO_2 production to confirm this hypothesis.

Moreover, we cannot exclude the contribution of the release of the hypoxic stimulus mediated by peripheral chemoreceptors on the decrease in $\dot{V}_E$. Changes in $\dot{V}_E$ may be influenced by changes in oxygenation when P_{aO_2} is < 100 mm Hg. The mean P_{aO_2} in our subjects in normoxia was 66 mm Hg, and therefore, a diminished hypoxic response could be involved in the decrease in $\dot{V}_E$ in our subjects. Unfortunately, we did not have the P_{aO_2} of our subjects in stable condition. We assumed that they were normoxic because no subject needed home oxygen therapy. However, eventual individual differences with study baseline P_{aO_2} could have altered subjects' respiratory drive.

The severity of airway obstruction did not appear to be correlated with the development of hyperoxia-induced hypercapnia in our subjects, as described previously.[7,26] In contrast, Sassoon et al[5] found a linear association between FEV_1 and changes in P_{aCO_2} with hyperoxia. These discrepancies may arise from the fact that our subjects were on mechanical ventilation with pressure support of 7 cm H_2O and were recovering from an exacerbation, whereas in the Sassoon study,[5] they were stable outpatients without respiratory assistance. However, our subjects showed a positive correlation between FEV_1 and hyperoxia-induced changes in $\Delta\dot{V}_E/\Delta P_{aCO_2}$, indicating that airway obstruction severity may affect the ventilatory response to hypercapnia without affecting respiratory drive.

Our mean increase in P_{aCO_2} with hyperoxia was 3 mm Hg, similar to that observed in other studies comparing normoxia and hyperoxia,[5,7] whereas this increase was $>$ 2-fold when comparing hypoxia with hyperoxia.[4,8] It is plausible that normoxia would reverse prior hypoxic pulmonary vasoconstriction, and further increases in F_{IO_2} should cause only a small increase in P_{aCO_2}. In fact, studies comparing normoxia and hyperoxia showed that hypercapnia did not happen in ready-to-wean, CO_2-retaining subjects with COPD.[11] Thus, in intubated, ready-to-wean patients with COPD, if a significant increase in P_{aCO_2} occurs, we should first think of other causes of acute hypercapnia, such as an increase in bronchospasm, the presence of fatigue, or the effect of sedatives rather than the effect of hyperoxia. In clinical practice, clinicians should try to keep patients with COPD in normoxia irrespective of their clinical status because, although discrete, hypercapnia occurs likewise.

Among the limitations of our study, we note the small sample size that confers small power to our results, with wide SD values principally in the CO_2 response indexes studied. In addition, it is possible that larger changes in P_{aCO_2} after breathing O_2 are required to demonstrate a significant relationship between changes in P_{aCO_2} and CO_2 response indexes.

Another limitation of the study is the interpretation of the CO_2 response test due to the differences in baseline P_{aCO_2} in normoxia and hyperoxia. This baseline difference could modify the respiratory response to hypercapnia and could mislead the interpretation of our results. However, owing to the linearity of the response described in the CO_2 response test, we think this would minimally affect our results.

The reliability of the CO_2 response test may be another limitation of the study. As described previously, the variability of CO_2 response test measurements offers moderate accuracy.[14,15] Although of value for investigation of respiratory drive, this test is exposed to an intrinsic variability due to many reasons, such as the large day-to-day intra-individual variation in breathing pattern parameters. However, the reproducibility of the test, which has been analyzed in our study, shows good precision, which may provide reliable results on the effects of hyperoxia.

Finally, we measured $\dot{V}_E$ and $P_{0.1}$ with a built-in ventilator function instead of the conventional method. This could overestimate high $P_{0.1}$ values or underestimate low $P_{0.1}$ values.[27]

Overall, our study shows the presence of hyperoxia-induced hypercapnia in normoxic, intubated COPD subjects with low inspiratory assistance and recovering from an exacerbation. According to our results, in this situation, a damped respiratory drive does not seem to be the major mechanism responsible for hyperoxia-induced hypercapnia. It most likely ultimately depends more on increased dead space, worsening ventilation-perfusion distribution, or the Haldane effect.

Conclusions

In summary, in normoxic subjects with COPD exacerbation during weaning from mechanical ventilation, hyperoxia does not seem to modify significantly the central respiratory drive or the ventilatory response to hypercapnia. Nonetheless, hyperoxia is followed by a

slight increase in P_{aCO_2}, probably due to alterations in ventilation/perfusion matching and the Haldane effect.

REFERENCES

1. Prime FJ, Westlake EK. The respiratory response to CO_2 in emphysema. Clin Sci 1954;13(3):321-332.
2. Campbell EJ. Respiratory failure: the relation between oxygen concentrations of inspired air and arterial blood. Lancet 1960;2(7140):10-11.
3. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne JP. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1980;122(2):191-199.
4. Aubier M, Murciano D, Milic-Emili J, Touaty E, Daghfous J, Pariente R, Derenne JP. Effects of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 1980;122(5):747-754.
5. Sassoon CS, Hassell KT, Mahutte CK. Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. Am Rev Respir Dis 1987;135(4):907-911.
6. Robinson TD, Freiberg DB, Regnis JA, Young IH. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161(5):1524-1529.
7. Dunn WF, Nelson SB, Hubmayr RD. Oxygen-induced hypercarbia in obstructive pulmonary disease. Am Rev Respir Dis 1991;144(3 Pt 1):526-530.
8. Dick CR, Liu Z, Sassoon CS, Berry RB, Mahutte CK. O_2-induced change in ventilation and ventilatory drive in COPD. Am J Respir Crit Care Med 1997;155(2):609-614.
9. Hanson CW 3rd, Marshall BE, Frasch HF, Marshall C. Causes of hypercarbia with oxygen therapy in patients with chronic obstructive pulmonary disease. Crit Care Med 1996;24(1):23-28.
10. Santos C, Ferrer M, Roca J, Torres A, Hernández C, Rodriguez-Roisin R. Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med 2000;161(1):26-31.
11. Crossley DJ, McGuire GP, Barrow PM, Houston PL. Influence of inspired oxygen concentration on deadspace, respiratory drive, and P_{aCO_2} in intubated patients with chronic obstructive pulmonary disease. Crit Care Med 1997;25(9):1522-1526.
12. Whitelaw WA, Derenne JP, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 1975;23(2):181-199.
13. Fernández R, Cabrera J, Calaf N, Benito S. $P_{0.1}/P_{IMax}$: an index for assessing respiratory capacity in acute respiratory failure. Intensive Care Med 1990;16(3):175-179.
14. Sahn SA, Zwillich CW, Dick N, McCullough RE, Lakshminarayan S, Weil JV. Variability of ventilatory responses to hypoxia and hypercapnia. J Appl Physiol 1977;43(6):1019-1025.
15. Lederer DH, Altose MD, Kelsen SG, Cherniack NS. Comparison of occlusion pressure and ventilatory responses. Thorax 1977;32(2):212-220.
16. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J 2007;29(5):1033-1056.
17. Sidney DA, Poon CS. Ventilatory responses to dead space and CO_2 breathing under inspiratory resistive load. J Appl Physiol 1995;78(2):555-561.
18. Ranieri VM, Giuliani R, Mascia L, Grasso S, Petruzzelli V, Puntillo N, et al. Patient-ventilator interaction during acute hypercapnia: pressure-support vs. proportional-assist ventilation. J Appl Physiol 1996;81(1):426-436.
19. Raurich JM, Rialp G, Ibáñez J, Campillo C, Ayestarán I, Blanco C. Hypercapnia test as a predictor of success in spontaneous breathing trials and extubation. Respir Care 2008;53(8):1012-1018.
20. Kuhlen R, Hausmann S, Pappert D, Slama K, Rossaint R, Falke K. A new method for $P_{0.1}$ measurement using standard respiratory equipment. Intensive Care Med 1995;21(7):554-560.
21. Fernandez R, Raurich JM, Mut T, Blanco J, Santos A, Villagra A. Extubation failure: diagnostic value of occlusion pressure ($P_{0.1}$) and $P_{0.1}$-derived parameters. Intensive Care Med 2004;30(2):234-240.
22. Alberti A, Gallo F, Fongaro A, Valenti S, Rossi A. $P_{0.1}$ is a useful parameter in setting the level of pressure support ventilation. Intensive Care Med 1995;21(7):547-553.
23. Brochard L, Rua F, Lorino H, Lemaire F, Harf A. Inspiratory pressure support compensates for the additional work of breathing caused by the endotracheal tube. Anesthesiology 1991;75(5):739-745.
24. Mehta S, Nelson DL, Klinger JR, Buczko GB, Levy MM. Prediction of post-extubation work of breathing. Crit Care Med 2000;28(5):1341-1346.
25. Luft UC, Mostyn EM, Loeppky JA, Venters MD. Contribution of the Haldane effect to the rise of arterial P_{CO_2} in hypoxic patients breathing oxygen. Crit Care Med 1981;9(1):32-37.
26. Lopez-Majano V, Dutton RE. Regulation of respiration during oxygen breathing in chronic obstructive lung disease. Am Rev Respir Dis 1973;108(2):232-240.
27. Subirana M, Irrazábal C, Bak E, Jara F, Mancebo J. Assessment of occlusion pressure measurement using standard respiratory equipment of Evita ventilators. Med Intensiva 1997;21(8):305-310.