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Helium-oxygen decreases inspiratory effort and work of breathing during pressure support in intubated patients with chronic obstructive pulmonary disease

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Abstract *Objective:* To evaluate the impact of helium-oxygen (He/O_2) on inspiratory effort and work of breathing (WOB) in intubated COPD patients ventilated with pressure support. *Design and setting:* Prospective crossover interventional study in the medical ICU of a university hospital. *Patients and participants:* Ten patients. *Interventions:* Sequential inhalation (30 min each) of three gas mixtures: (a) air/O_2, (b) He/O_2 (c) air/O_2, at constant FIO_2 and level of pressure support. *Measurements and results:* Inspiratory effort and WOB were determined by esophageal and gastric pressure. Throughout the study pressure support and FIO_2 were 14±3 cmH_2O and 0.33±0.07 respectively. Compared to Air/O_2, He/O_2 reduced the number of ineffective breaths (4±5 vs. 9±5 breaths/min), intrinsic PEEP (3.1±2 vs. 4.8±2 cmH_2O), the magnitude of negative esophageal pressure swings (6.7±2 vs. 9.1±4.9 cmH_2O), pressure-time product (42±37 vs. 67±65 $cmH_2O\ s^{-1}\ min^{-1}$), and total WOB (11±3 vs. 18±10 J/min). Elastic (6±1 vs. 10±6 J/min) and resistive (5±1 vs. 9±4 J/min) components of the WOB were decreased by He/O_2. *Conclusions:* In intubated COPD patients ventilated with pressure support He/O_2 reduces intrinsic PEEP, the number of ineffective breaths, and the magnitude of inspiratory effort and WOB. He/O_2 could prove useful in patients with high levels of PEEPi and WOB ventilated in pressure support, for example, during weaning.

Keywords Helium · Heliox · Pressure support · Mechanical ventilation · Work of breathing

Introduction

In decompensated chronic obstructive pulmonary disease (COPD) there is a marked increase in both the elastic and resistive components of the work of breathing (WOB) [1, 2, 3]. The ensuing respiratory muscle fatigue is a key factor determining weaning trial failure [4, 5], and prolonged ventilator dependence [1] in intubated patients. Pressure support (PS) is often used to provide a titrable level of respiratory muscle unloading in these patients [1]. However, excessive levels of PS can adversely affect patient-ventilator synchrony and increase WOB [6, 7]. Likewise, applying external positive end-expiratory pressure (PEEPe) can offset the inspiratory threshold effect of intrinsic PEEP (PEEPi) [8], but PEEPe may be difficult to titrate and can increase total PEEP and dynamic hyperinflation [9, 10]. On the other hand, helium-oxygen (He/O_2) reduces the resistance to flow within the airways due to its low density [11]. In turn this effect has been shown to enhance lung emptying and decrease PEEPi [12] and to reduce WOB during controlled mechanical ventilation [13] and T-piece breathing [14] in intubated COPD. However, while two studies have shown that He/O_2 can exert such beneficial effects in acutely decompensated COPD patients undergoing noninvasive PS [15, 16], no study has so far addressed whether these beneficial effects could also be observed in intubated patients. Such a favorable impact might indeed improve

patient tolerance and endurance to spontaneous-assisted ventilation, for example, during weaning, while avoiding the deleterious effects of excessive respiratory muscle loading [17]. The purpose of the present study was therefore to test the hypothesis that He/O_2 can reduce PEEPi and the magnitude of inspiratory effort and WOB during PS in intubated COPD patients.

Results from this study were presented in abstract form at the 2005 annual meeting of the American Thoracic Society [18].

Patients and methods

Patients

Patients were consecutively included if they met the commonly accepted criteria for COPD [19], were intubated, and in PS mode. Exclusion criteria were the presence of pneumothorax and/or hypoxemia requiring an inspired O_2 fraction (FIO_2) of 0.45 or higher. Ten patients were consecutively included in the study; patients' main clinical characteristics are summarized in Table 1. Data collection was complete in all patients. As seen in their most recent FEV 1.0 values from the 2 years prior to admission, patients had severe obstructive disease. The protocol was accepted by the Ethics committee of our institution. Informed consent was obtained from all patients.

Methods

Prior to protocol initiation a nasogastric tube with esophageal and gastric balloons (Guenard ch 16 nasogastric tube, Marquat Génie Biomédical, Boissy-Saint-Léger, France) was inserted, and its correct position verified by the occlusion method [20]. The electromyographic activity of the diaphragm (EMGd) was recorded with two surface electrodes positioned on the right and left costal margins with a reference electrode placed over the sternum [21]. After filtering and digitalization at a sampling rate of 1000 Hz by means of the Biopac EMG module (Biopac Systems, Goleta, Calif., USA) the EMGd signal was rectified and integrated [22].

Patients were placed in a semirecumbent position, and the protocol was initiated after tracheal suctioning. All patients were ventilated with a Galileo Gold Series ventilator (Hamilton Medical, Rhäzuns, Switzerland), which can be safely used to deliver He/O_2 without any modifications [23]. He/O_2 was administered as previously described [12, 16]. Briefly, a 50-l canister pressurized at 200 bar (Carbagas, Gümligen, Switzerland) containing a 78:22 mixture of He and O_2 was connected through a pressure regulator at 6 bar into the ventilator's air inlet. A correction factor for reported tidal volume (VT) was used, since the VT reading on the ventilator underestimates the actual VT during He/O_2 use [23]. The VT computed with this correction factor was also checked against true VT measured with a precision density-independent spirometer (5420 Volume Monitor, Ohmeda, Louisville, Col., USA). A heat and moisture exchanger was fitted on the ventilator circuit between the endotracheal tube and the Y-piece in all patients-PS was set by the clinician in charge of the patient, following our usual practice guidelines, i.e., FIO_2 adjusted to maintain SpO_2 at a level higher than 0.9, level of PS titrated to obtain an expired VT of 8 ml/kg, pressurization time of 0.2 s, inspiratory trigger set at maximum sensitivity, and inspiratory:expiratory cycling set at 25% of peak inspiratory flow rate. PEEPa to compensate for the inspiratory threshold load of PEEPi was added following our usual protocol, i.e., starting at zero end-expiratory pressure and increasing by 1 cmH_2O increments until ineffective inspiratory attempts disappeared or decreased [8] to a maximum of 10 cmH_2O.

After an initial 30 min period with Air/O_2 patients were switched to the He/O_2 mixture for 30 min, then back again for 30 min to Air/O_2. All ventilator settings including FIO_2 were kept constant throughout the protocol. Heart rate, arterial blood pressure, and pulse oxymetry were continuously monitored.

Measurement protocol

Data recordings were performed during the last 5 min of ventilation with each gas mixture. Esophageal (P_{es}) and gastric pressures (P_{ga}) were continuously recorded by differential pressure transducers (Biopac), all signals being digitalized at a sampling rate of 1000 Hz, and stored in a laptop computer for subsequent analysis (AcqKnowledge software, Biopac). Patient inspiratory effort time (ti) was measured as the interval between the initial decrease in P_{es} and the initial rapid decrease of electrical activity on the processed EMGd signal [22, 24].

The following parameters were determined during each phase of the protocol: VT, minute-volume ($V'E$), and peak expiratory flow (V'_{exp}) obtained by analysis of the instantaneous flow tracing; peak expiratory resistance (R_{exp}) computed as $R_{exp}=P_{aw}-P_{es}/V'_{exp}$, where P_{aw}=airway pressure; the expiratory time constant (τe), de-

Table 1 Main clinical characteristics and initial ventilator settings (*BW* body weight, *FEV1.0* last documented value of 1-s forced expiratory volume in absolute value and percentage of predicted value, *FIO_2* inspired O_2 fraction, *PS* level of pressure support above PEEPe, *PEEPe* level of externally applied positive end-expiratory pressure)

Patient no.	Age (years)	Sex	BW (kg)	FIO_2	FEV1.0 (l; % pred	PS (cmH_2O)	PEEPe (cmH_2O)
1	77	M	55	0.25	0.60 (20)	11	7
2	57	M	65	0.25	–	14	7
3	65	M	47	0.30	–	12	10
4	77	M	60	0.40	0.76 (19)	13	6
5	78	M	67	0.25	–	14	5
6	71	M	60	0.40	1.12 (42)	12	5
7	77	F	56	0.40	0.44 (26)	15	10
8	75	F	57	0.40	0.68 (32)	12	5
9	60	M	68	0.35	0.57 (20)	18	8
10	50	F	50	0.35	–	22	10
mean	68.7		58.5	0.33	0.69/26	14.3	7.3
(SD)	(10.1)		(6.9)	(0.07)	(0.23)/(9)	(3.4)	(2.1)

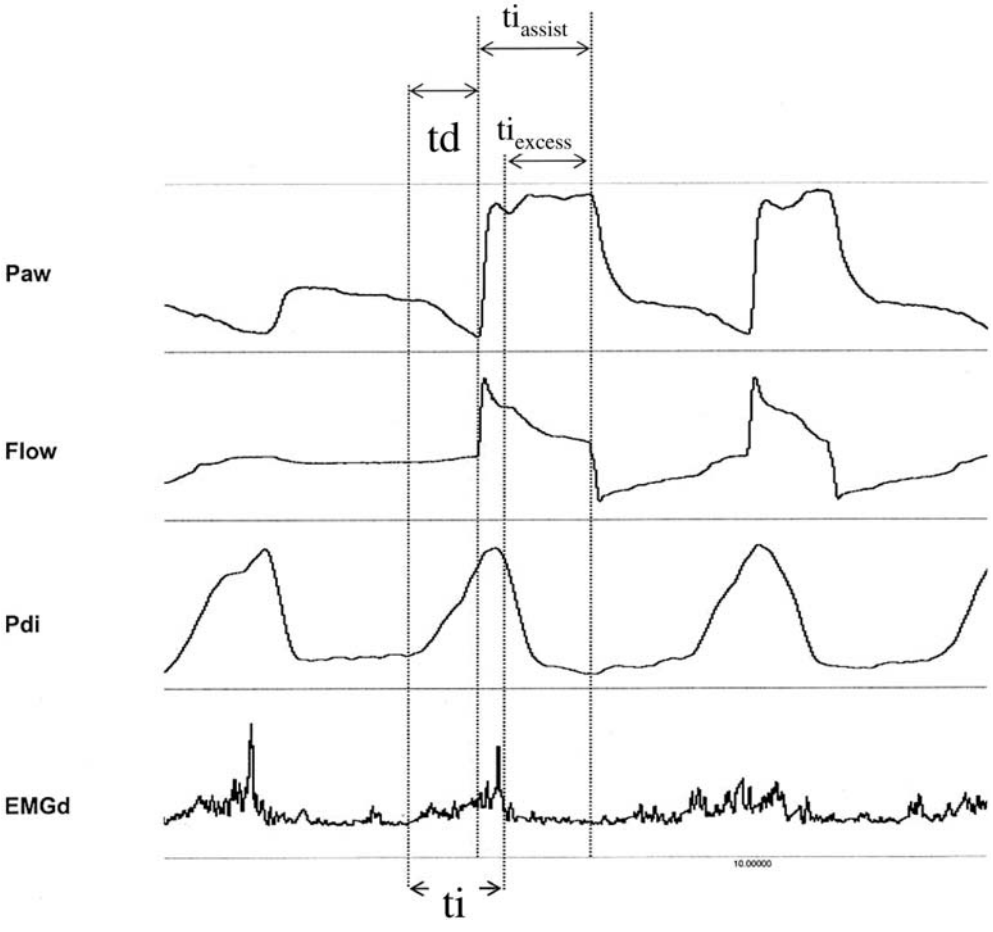

Fig. 1 Representative tracing from a patient, illustrating the various time intervals used. *Paw* Airway pressure; *Flow* instantaneous flow measured at airway opening; *Pdi* transdiaphragmatic pressure; *EMGd* electromyographic recording of the diaphragm; *td* trigger delay; *ti* patient inspiratory effort duration; ti_{assist} duration of pressurization by the ventilator; ti_{excess} duration of pressurization by the ventilator extending beyond the end of ti

termined by analysis of the expiratory flow-volume tracing [25]; respiratory rate reported by the ventilator (RR_{vent}); patient respiratory rate (RR_{pat}) determined from EMGd and P_{es} tracings; number of ineffective inspiratory attempts (R_{ineff}), computed as $R_{ineff}=RR_{pat}-RR_{vent}$; PEEPi: the P_{es} difference between the onset of inspiratory effort and the point at which instantaneous expiratory flow reached 0, further corrected for any expiratory muscle activity [26]; trigger delay (Td): the time difference between the onset of inspiratory effort and that of pressurization by the ventilator; duration of delayed cycling (ti_{excess}), computed as the difference between the end of ti and the duration of pressurization by the ventilator. Respiratory muscle workload can be determined by two approaches. One is to compute it from the esophageal pressure and flow tracings. Its drawback is that it is dependent on flow, and therefore does not take into account the ineffective inspiratory efforts which are often present in COPD. Hence this technique underestimates the magnitude of inspiratory muscle workload. However, its main advantage is that it allows determination of total transpulmonary WOB and its partition into elastic and resistive components, which is important to assess the various effects of helium in obstructive patients. The other approach is to compute the pressure-time product, which does not depend on flow, and therefore takes into account the workload imposed by ineffective inspiratory attempts. This technique is also well correlated with respiratory muscle oxygen consumption and therefore with the metabolic cost of breathing. We therefore used both methods in the present study. Inspiratory WOB was determined by analysis of the P_{es}–VT tracing, using the classical method based on the Campbell diagram [15, 27]: briefly, WOB was determined as the area enclosed between (a) the inspiratory P_{es}–VT curve and (b) the static esophageal chest wall pressure-volume curve, using a theoretical chest wall compliance value (4% of the predicted value of the vital capacity/cmH_2O). WOB was expressed as work per breath (J/cycle) and per volume unit (J/l).

Using measurements of transpulmonary pressure (i.e., the difference between airway pressure, Paw, measured at the endotracheal tube, and P_{es}), total transpulmonary work per minute (Wtp_{tot}, J/min) was determined, and partitioned into its resistive (Wtp_{res}, J/min) and elastic (Wtp_{el}, J/min) components [15]. Finally, due to the presence of ineffective inspiratory attempts inspiratory effort was also quantified by computation of transdiaphragmatic pressure (P_{di}), as well as total (PTP_{di}) and triggering (PTP_t) pressure-time products, which are independent of flow and volume signals [28]. WOB was thus computed only for those patient breaths which triggered the ventilator, as was the PTP_t, while P_{di} and PTP_{di} were determined for both triggering and nontriggering breaths. Arterial blood gases were analyzed at the end of each study phase. Figure 1 illustrates the various time intervals from a patient.

Statistics

Data are expressed as mean ±standard deviation. Comparisons (SigmaStat 2.0, SPSS Science) between the three conditions was made by analysis of variance, significance between the time points being determined by Fisher's protected least significance test. A p value less than 0.05 was considered significant.

Table 2 Patients' respiratory pattern and mechanics [IE_{ineff} ineffective inspiratory efforts (IE_{ineff}=RR_{pat}–RR_{vent}), *PEEPi* intrinsic positive end-expiratory pressure, R_{exp} peak expiratory resistance computed as R_{exp}=(airway–esophageal pressure)/peak expiratory flow, RR_{pat} patient respiratory rate, RR_{vent} respiratory rate reported by the ventilator, *VT* tidal volume, *VE* minute ventilation, *ti* duration of patient inspiratory effort, V'_{exp} peak expiratory flow, τe expiratory time constant, ti_{excess} duration of pressurization by the ventilator extending beyond the end of ti, *td* trigger delay (time between onset of ti and onset of pressurization by the ventilator)]

	Air/O_2 1	He/O_2	Air/O_2 2
RR_{vent} (b/min)	16±3.6	13.1±3.1*	16.2±3.9
RR_{pat} (b/min)	23.6±6.1	19.2±5.4*	23±5.2
IE_{ineff} (b/min)	9±5	4±5*	6.2±4
V_T (l)	0.601±0.228	0.621±0.276	0.611±0.258
VE (l/min)	9.04±2.8	8.25±5.3	9.40±3.5
ti (s)	0.688±0.23	0.704±0.23	0.728±0.254
td (s)	0.489±0.241	0.472±0.229	0.511±0.243
ti_{excess} (s)	0.899±0.36	0.876±0.384	0.873±0.377
PEEPi (cmH_2O)	4.8±2.7	3.1±2.7*	5±2.6
V'_{exp} (l/s)	0.63±0.18	0.89±0.66*	0.62±0.18
τe(s)	2.06±0.93	1.42±0.88**	2.06±0.94
R_{exp} ($cmH_2O\ l^{-1}s^{-1}$)	29.7±11	22.5±9*	29.6±10

* $p<0.05$ vs. AirO_2 1 and AirO_2 2, ** $p<0.01$ vs. AirO_2 1 and AirO_2 2 (analysis of variance)

Table 3 Patients' inspiratory effort and work of breathing [$\Delta Peso$ magnitude of esophageal pressure swings, ΔPdi magnitude of transdiaphragmatic pressure swings, PTP_{eso} esophageal pressure-time product expressed per cycle and time unit, PTP_t triggering pressure-time product per cycle, W_{eso} work of breathing derived from esophageal pressure tracing expressed per cycle and time unit, *Wtp* total (*tot*), resistive (*res*), and elastic (*el*) work of breathing derived from transpulmonary pressure measurements)

	Air/O_2 1	He/O_2	Air/O_2 2
ΔPeso (cmH_2O)	9.1±4.9	6.7±2*	8.9±5
ΔPdi (cmH_2O)	6.8±5.9	5.7±2.5*	6.7±5.1
PTP_{eso}/cycle (cmH_2O/s)	4.1±3.6	2.5±2.4*	4.3±3.9
PTP_{eso}/min ($cmH_2O\ s^{-1}\ min^{-1}$)	67.1±65	41.8±37.4*	69.7±66.1
PTP_t/cycle (cmH_2O/s)	2.2±1.5	1.5±0.8*	2.1±1.7
W_{eso}/cycles (J/cycle)	0.253±0.30	0.105±0.098*	0.260±0.3
W_{eso}/min (J/min)	4.2±5.8	1.7±1.5*	4.2±5.8
Wtp_{tot} (J/min)	18.2±10.7	10.7±3.5*	18.2±10.6
Wtp_{res} (J/min)	8.51±4.4	4.9±1.1*	8.46±4.3
Wtp_{el} (J/min)	10.3±6.5	6.1±1.3*	10.2±6.5

* $p<0.05$ vs. AirO_2 1 and AirO_2 2 (analysis of variance)

Results

No significant differences were observed between the Air/O_2 1 and Air/O_2 2 data sets. The patients' respiratory pattern for each condition are shown in Table 2. Expiratory resistance, expiratory time constant, and peak expiratory flow all decreased with He/O_2. PEEPi was present in all patients, and its magnitude was decreased by He/O_2 as well as the number of ineffective inspiratory attempts. Delayed cycling (ti_{excess}) was present in all patients but was not influenced by He/O_2. Table 3 summarizes the main findings with respect to inspiratory effort and WOB. The magnitude of inspiratory effort, characterized by the P_{es} and P_{di} variations, was decreased by He/O_2, as was the PTP. The individual variations or P_{di} swings are shown in Fig. 2. The total WOB determined from the P_{es} tracing was reduced during He/O_2 inhalation. Finally, WOB computed from the transpulmonary pressure measurements was also decreased by He/O_2, in both its elastic and its resistive components. As shown in Table 4, He/O_2 had no effect on arterial blood gases or hemodynamics.

Discussion

The findings of the present study demonstrate that in intubated patients with severe COPD ventilated in PS He/O_2 decreases the level of PEEPi and the number of ineffective inspiratory attempts and also reduces the magnitude of inspiratory efforts and the total WOB as well as its resistive and elastic components. Let us now attempt to put these results in perspective and assess how they may affect the weaning process in COPD patients.

Several limitations of the study should be noted initially. First, only a small number of patients was studied. However, all patients exhibited the same response pattern when switched from one gas mixture to another. Second, the static esophageal chest wall pressure-volume curve was determined using a theoretical chest wall compliance

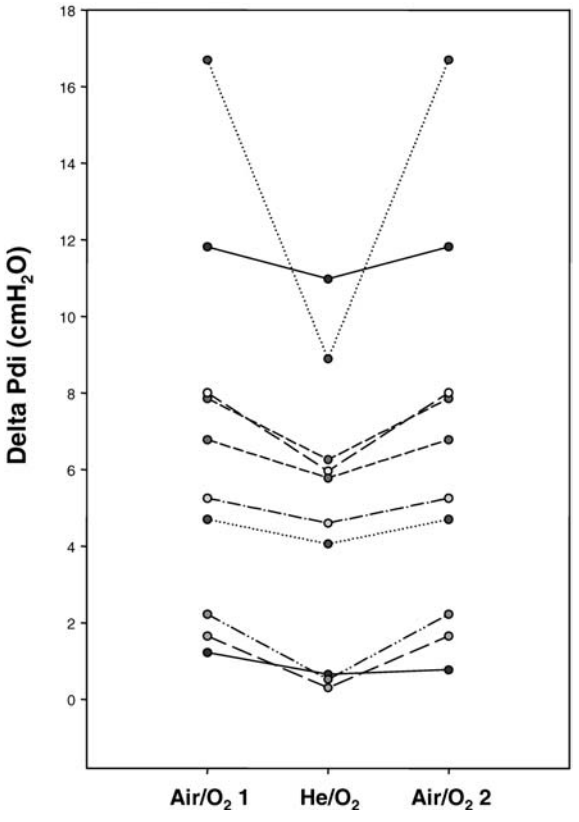

Fig. 2 Individual variations in transdiaphragmatic pressure swings during the three phases of the study

Table 4 Arterial blood gases and hemodynamics; all differences nonsignificant (*HR* heart rate, *MAP* mean arterial pressure, PaO_2 arterial partial pressure of O_2, $PaCO_2$ arterial partial pressure of CO_2, SaO_2 O_2 saturation of arterial blood)

	Air/O_2 1	He/O_2	Air/O_2 2
pH	7.39±0.09	7.37±0.05	7.38±0.07
$PaCO_2$ (torr)	51±4	52±2	52±3
PaO_2 (torr)	71±5	74±3	74±4
SaO_2 (%)	98±0.9	98±1.7	98±0.6
HR (n/min)	83±19	82±17	83±18
MAP (mmHg)	85±13	86±12	87±12

rather than a measured value. Nonetheless, although some degree of error can occur with this approach, comparisons between those conditions remains valid, given that the error is present in all measurement conditions [27]. Third, He/O_2 was administered for 30 min, which might be insufficient for its full effects to occur in very inhomogeneous lungs such as those of COPD. However, this duration is in line with that of other studies in which a highly significant effect of He/O_2 was documented after 20–45 min [10, 12, 13, 14, 15, 16]. Fourth, during spontaneous-assisted breathing reliable measurements of static respiratory system compliance are not possible, leading to some difficulties in interpreting changes in the elastic component of the WOB (Wtp_{el}) [13].

Overall our findings are in line with those of recent studies on He/O_2 in intubated COPD patients. During controlled ventilation a decrease in dynamic hyperinflation and PEEPi with He/O_2 has been shown [10, 12]. The level of PEEPi was lower in the present study, which is to be expected as patients were in the weaning phase, whereas those of the two former studies had been intubated for less than 48 h. However, the magnitude of decrease in PEEPi was comparable between these three studies. Recently Gainnier et al. [13] obtained similar results in patients undergoing controlled ventilation and also documented a reduction in total, resistive, and elastic WOB with He/O_2. The magnitude of decrease in total and individual determinants of WOB was greater in our patients, although the ventilatory mode and timing with regards to intubation were different. This discrepancy probably results from the different measurement techniques used as well as from the fact that their patients were in controlled conditions while those of the present study were undergoing PSV.

In spontaneously breathing COPD patients immediately before extubation without any ventilatory assistance Diehl et al. [14] also observed that He/O_2 reduced the level of PEEPi and the WOB, mainly of its resistive component. PEEPi was lower than that in our patients, which is to be expected given that the Diehl et al. study was performed immediately before extubation. Likewise, and probably for the same reasons, the reduction in WOB was smaller in the patients studied by Diehl et al. Finally, during noninvasive PSV applied by face mask to acutely decompensated patients He/O_2 leads to a reduction in WOB [15], $PaCO_2$, and dyspnea [15, 16]. Jaber et al. [15] found that PSV at levels comparable to that in our patients decreased the intensity of inspiratory efforts and WOB. The magnitude of these changes was close to that observed in our patients, although PSV was applied noninvasively and to acutely decompensated patients.

The effects of He/O_2 on the patients' ventilatory pattern should be briefly discussed. First, one might have expected the triggering delay to decrease while breathing He/O_2, as PEEPi, which represents an inspiratory threshold load, was reduced. The fact that only a nonsignificant trend towards a lower delay was documented probably stems from the low initial level of PEEPi in our patients. Delayed cycling was unaffected by He/O_2. This is not surprising given that delayed cycling is influenced by several factors such as the cycling cutoff level of the ventilator (25% of peak inspiratory flow in this study), the time constant of the respiratory system (RC), duration and magnitude of inspiratory effort, level of PS, and profile of the pressure-time curve [22, 29]. Quantitatively the most important determinant of delayed cycling is the ratio between RC and inspiratory time [22, 29]. While elastance and resistance were not measured, the decrease in elastic

and resistive components of the WOB suggests that both determinants of the RC were reduced, and therefore that RC remained unchanged. Inspiratory time was also unchanged. Therefore no modification in the magnitude of delayed cycling was observed, as one would expect.

Of note, no effect of He/O_2 on $PaCO_2$ was observed. However, the key factor determining the impact of heliox on $PaCO_2$ is probably its initial level. In a previous study in patients undergoing noninvasive PS we found that $PaCO_2$ was lowered the most in those patients who had the highest initial levels of hypercapnia [16], a finding which has subsequently been confirmed by Jaber et al. [15]. In the present study the patients were not acutely decompensated or severely hypercapnic but represented a heterogeneous group of patients who had been intubated, ventilated in controlled mode, and at various stages of the weaning process in PS. Therefore some patients were nonhypercapnic while others had no elevation or only moderate increases in $PaCO_2$. Illustrating this point, we found no effect on $PaCO_2$ in patients without marked hypercapnia in two studies in intubated patients undergoing controlled ventilation [10, 12].

Our results confirm that He/O_2, by reducing expiratory airways resistance, can increase expiratory flow, thereby leading to enhanced lung emptying and a decrease in PEEPi. This in turn leads to several beneficial effects. First, the decreased inspiratory threshold load induces a reduction in the number of nontriggering breaths and most likely accounts for the decrease in the magnitudes of esophageal pressure swings and PTP. Second, through the reduction in PEEPi and airways resistance there is a decrease in both elastic and resistive WOB. These results add to the body of evidence outlining the favorable pathophysiological effects of He/O_2 in COPD and suggests that it may be useful in difficult-to-wean patients. However, to date there is no proof that these effects can actually impact patient outcome [30]. Furthermore, He/O_2 can interfere with ventilator function, thus requiring thorough knowledge of these technical aspects by intensivists to ensure patient safety [23]. Finally, cost can be an issue, although probably not a major one [30].

In conclusion, the present study demonstrates that in intubated COPD patients ventilated with PS He/O_2 enhances lung emptying, decreases PEEPi and the number of ineffective inspiratory attempts, and reduces the various key determinants of elevated WOB and inspiratory effort. He/O_2 may therefore prove useful in patients with high levels of PEEPi and WOB by unloading the respiratory muscles. This can improve patient-ventilator interaction and tolerance to spontaneous-assisted breathing, which in turn may be beneficial for patient outcome, for example, by facilitating weaning. However, the optimal timing and duration of He/O_2 administration remains to be determined. Furthermore, given the technical pitfalls and cost issues associated with the use of He/O_2, studies are needed to determine whether the beneficial pathophysiologocal effects of He/O_2 inhalation during weaning can have an impact on the duration of weaning, ICU stay, and overall patient outcome.

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