

The Effects of High-Flow vs Low-Flow Oxygen on Exercise in Advanced Obstructive Airways Disease*

Wissam Chatila, MD; Tom Nugent, MD; Gwendolyn Vance, RN; John Gaughan, PhD; and Gerard J. Criner, MD

Study objectives: Current options to enhance exercise performance in patients with COPD are limited. This study compared the effects of high flows of humidified oxygen to conventional low-flow oxygen (LFO) delivery at rest and during exercise in patients with COPD.

Design: Prospective, nonrandomized, nonblinded study.

Setting: Outpatient exercise laboratory.

Patients: Ten patients with COPD, stable with no exacerbation, and advanced airflow obstruction (age, 54 ± 6 years; FEV₁, $23 \pm 6\%$ predicted [mean \pm SD]).

Interventions: After a period of rest and baseline recordings, patients were asked to exercise on a cycle ergometer for up to 12 min. Exercising was started on LFO first; after another period of rest, the patients repeated exercising using the high-flow oxygen (HFO) system, set at 20 L/min and matched to deliver the same fraction of inspired oxygen (FIO₂) as that of LFO delivery.

Measurements and results: Work of breathing and ventilatory parameters (tidal volume, respiratory rate, inspiratory time fraction, rapid shallow breathing index, pressure-time product) were measured and obtained from a pulmonary mechanics monitor. Borg dyspnea scores, pulse oximetry, blood gases, vital signs were also recorded and compared between the two delivery modes. Patients were able to exercise longer on high flows (10.0 ± 2.4 min vs 8.2 ± 4.3 min) with less dyspnea, better breathing pattern, and lower arterial pressure compared to LFO delivery. In addition, oxygenation was higher while receiving HFO at rest and exercise despite the matching of FIO₂.

Conclusion: High flows of humidified oxygen improved exercise performance in patients with COPD and severe oxygen dependency, in part by enhancing oxygenation.

(*CHEST* 2004; 126:1108–1115)

Key words: chronic bronchitis; emphysema; exercise; hyperoxia; work of breathing

Abbreviations: FIO₂ = fraction of inspired oxygen; HFO = high-flow oxygen; LFO = low-flow oxygen; RR = respiratory rate; SpO₂ = oxygen saturation; Ti/TOT = inspiratory time fraction; VE = minute ventilation; Vt = tidal volume; WOB = work of breathing

Patients with COPD are frequently limited in their ability to perform exercise. Factors contributing to poor exercise tolerance in patients with COPD

have been attributed to abnormal lung mechanics, hypoxemia, deconditioning, and peripheral muscle dysfunction.^{1,2} Patients requiring a high fraction of inspired oxygen (FIO₂) are hampered by the available oxygen delivery systems. Virtually all patients with COPD receiving supplemental oxygen use the nasal cannula, a low-flow system geared to the oxygen requirement at rest and with limited activity. However, at high flows (≥ 6 L/min), the nasal cannula is poorly tolerated because of nasal dryness, crusting, and epistaxis.³ The other alternative to high-flow oxygen (HFO) for outpatient COPD is transtracheal oxygen delivery, which is limited by the patient's acceptance and potential complications.⁴ Although most patients receiving long-term oxygen therapy do not exceed the FIO₂ requirement delivered via the conventional nasal cannula, the oppor-

*From the Division of Pulmonary & Critical Care Medicine, Department of Medicine; Temple University School of Medicine, Philadelphia, PA.

Dr. Criner served as a consultant to the Food and Drug Administration for Vapotherm, Inc., in 2002, and received less than \$2,000 for compensation. Dr. Criner does not own stock in the company.

Manuscript received December 19, 2003; revision accepted April 26, 2004.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Wissam Chatila, MD, Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, 763 PP, Temple University School of Medicine, 3401 N Broad St, Philadelphia, PA 19140; e-mail: chatilw@tuhs.temple.edu

tunity to increase oxygen delivery during strenuous activities, *eg*, pulmonary rehabilitation, may enhance cardiovascular fitness and improve dyspnea during activities.

In this study, we evaluated the cardiopulmonary effects of delivering humidified HFO at rest and during exercise in patients with severe COPD, while comparing it to conventional low-flow oxygen (LFO) delivery. We used a Vapotherm HFO delivery source (Vapotherm; Annapolis, MD), a novel device that combines oxygen, pressurized air, and warm humidification in order to deliver tolerable flow rates reaching up to 40 L/min through a nasal cannula.

MATERIALS AND METHODS

Subjects

We recruited 10 patients with severe COPD from our outpatient pulmonary clinic. COPD was diagnosed by clinical history, and was confirmed by pulmonary function testing as per Global Initiative for Chronic Obstructive Lung Disease criteria.⁵ Patients with known cardiovascular disease were excluded. Patients completed the study during a period of clinical stability and no recent exacerbations for > 3 months. All patients signed an informed consent that was approved by the Institutional Review Board.

Study Design

Patients exercised while receiving oxygen via conventional LFO delivery then HFO after a period of rest (Fig 1). After

completing the setup, patients rested for 5 min while receiving LFO delivered via the mouthpiece, which was then followed by exercise up to 12 min as tolerated. Patients then rested for 30 min while receiving oxygen delivered via a nasal cannula, and then resumed the same rest-exercise protocol but with the Vapotherm device serving as HFO source. The exercise portion of the study was completed with the patient riding an unloaded bicycle. During the first 6 min of bicycle exercise, the patients sustained a tire rotational speed of 40 to 50 cycles per minute, and then were instructed to increase to 60 to 70 cycles per minute for the remainder of the exercise, to a maximum of 12 min, or to a time determined by exercise limitation if they were unable to cycle for 12 min.

Patient Setup

While seated in a chair, each subject had an esophageal balloon placed. The esophageal catheter (SmartCath Esophageal Catheter; Bicore; Irvine, CA) was placed via a nasoesophageal approach after instillation of 1% viscous lidocaine. The catheter was connected to a pulmonary mechanics monitor (Bicore CP-100; Bicore) to provide real-time display of various breathing parameters that were directly captured on a printer. Optimal positioning of the esophageal balloon was performed by monitoring the catheter pressure measurements during tidal breathing in the sitting position.⁶ The catheter was secured by tape to the patient's nose after confirmation of appropriate pressure tracings. The patients breathed through a mouthpiece connected to a VarFlex flow transducer (Gear Medical Systems; Palm Springs, CA) with their noses occluded by a clip; patients did not receive nasal oxygen with a nose clip on. The flow transducer was connected to the pulmonary mechanics monitor, which performed automated balloon testing and calibration prior to each round of exercise. The oxygen source was connected to the expiratory end of the flow transducer (*ie*, opposite to the mouthpiece) via a side port attached to extension tubing (Fig 1).

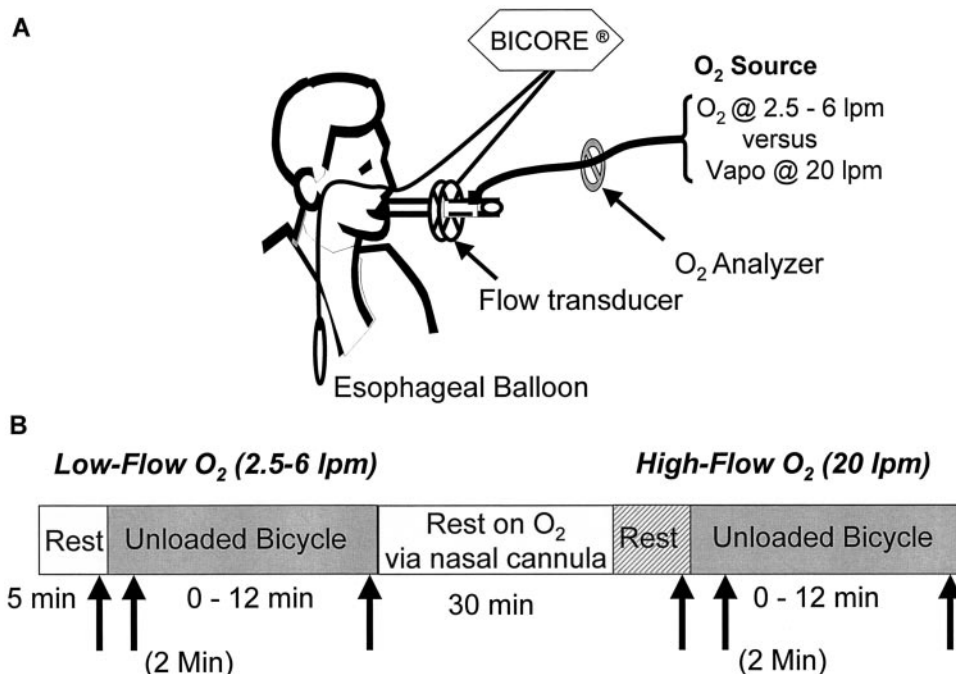


FIGURE 1. Patients rested and exercised first receiving LFO, which was then followed by a period of 30 min of rest while receiving oxygen delivered via nasal cannula. The protocol was then repeated with the Vapotherm device (Vapo) as the source for HFO delivery. The times when arterial blood gases were collected are indicated using arrows. lpm = liters per minute.

Flow and FIO_2 were set according to a previously determined oxygen titration test if available, or an arbitrarily chosen level of 2.5 to 6 L/min, hence starting at an FIO_2 of 28 to 60% at the beginning of the protocol, measured by an oxygen analyzer (MaxO₂; Max Tec; Salt Lake City, UT). The HFO system was adjusted to deliver an aggregate of 20 L/min of humidified gas (oxygen to ambient air mixture of 2 to 6 L/min blended with 14 to 18 L/min, respectively) warmed to 36°C. The Vapotherm HFO device attaches to an IV pole and uses membrane technology to warm and saturate the gas stream almost free of condensation at high flows at or above body temperature to deliver 40 to 55 mg of water per liter, usually via a small nasal cannula or transtracheal cannula. The air-oxygen mixture in the Vapotherm HFO device was titrated to deliver an FIO_2 that matches exactly the starting LFO FIO_2 for each patient. The patients remained receiving the same FIO_2 and flow rate as was set during the resting portion of the study, unless their oxygen saturation (SpO_2) decreased to < 90%. Any desaturations during exercise resulted in a compensatory increase in oxygen flow, hence FIO_2 , in order to maintain an $\text{SpO}_2 \geq 90\%$.

Data Collection

Measured variables taken from the pulmonary mechanics monitor were tidal volume (V_T), respiratory rate (RR), minute ventilation (\dot{V}_E), and work of breathing (WOB), inspiratory time fraction (T_I/T_{TOT}), rapid shallow breathing index (RR/V_T), pressure-time product, and change in esophageal pressure. Data collection at rest and during exercise were captured real time on a printer, and the mean of each variable was obtained during the last 20 s of every minute during exercise. In addition, BP, heart rate, modified Borg dyspnea score, and SpO_2 were recorded every minute. A minute-to-minute recording of tire revolutions per minute was made, ensuring no difference between LFO and HFO protocols. Three patients consented to an arterial line and provided a total of six arterial blood gases each (Fig 1, *bottom, B*).

Statistical Analysis

All data were analyzed on a minute-to-minute basis. Recordings from the pulmonary mechanics monitor were averaged over a 20-s period at the end of each minute and entered as representative data for that minute. Total exercise time using LFO and HFO was compared using a paired Student *t* test. All other parameters were compared using a mixed-model analysis of variance of a two-factor trial with repeated measures on the second factor, time, modeled with an autoregressive covariance structure.⁷ A $p < 0.05$ was considered significant, and all displayed *p* values for each variable represent treatment effect.

RESULTS

Eight of the 10 patients had complete collection of all respiratory parameters. Respiratory data for two patients were incomplete due to flow transducer malfunction in one patient, and displacement of the esophageal balloon during the protocol in the other patient. Table 1 shows baseline characteristics of the 10 patients.

HFO vs LFO at Rest

Patients receiving LFO received 3.9 ± 1.8 L/min (mean \pm SD), resulting in an FIO_2 of $39 \pm 11\%$,

Table 1—Patient Characteristics (n = 10)*

Variables	Mean \pm SD
Age, yr	54 \pm 6
Body mass index	25.0 \pm 4.6
FEV ₁	
L/s	0.74 \pm 0.19
% predicted	23 \pm 6
FVC	
L/s	2.51 \pm 0.67
% predicted	57 \pm 14
FEV ₁ /FVC	30 \pm 9
Residual volume	
L	4.96 \pm 1.58
% predicted	247 \pm 68
TLC	
L	7.56 \pm 1.62
% predicted	126 \pm 16
DLCO, % predicted	34 \pm 10
Oxygen needs at rest, L/min	2.2 \pm 1.6

*DLCO = diffusion capacity of the lung for carbon monoxide.

whereas they all received 20 L/min of HFO with the adjusted oxygen-air mixture, delivering an FIO_2 of $39 \pm 11\%$. Despite the equivalent FIO_2 , oxygenation was better with HFO (SpO_2 , $98 \pm 2\%$ vs $95 \pm 3\%$ [$p = 0.04$, $n = 10$]; and PaO_2 , 128 ± 34 mm Hg vs 74 ± 6 mm Hg [$p = 0.05$, $n = 3$]), but pH and PaCO_2 were not different (Fig 2). There was no difference between HFO and LFO delivery in all measured respiratory variables, heart rate, BP, and dyspnea score at rest (Figs 3–5).

HFO vs LFO During Exercise

While exercising receiving LFO, three patients had their oxygen flows increased due to $\text{SpO}_2 < 90\%$ (from a mean of 2.8 ± 0.3 to 9.6 ± 6.5 L/min, for these three patients), resulting in an increase of in FIO_2 from 30 to 56%. In contrast, no flow adjustments of oxygen were needed using the HFO device. Oxygenation, but not PaCO_2 or pH, was higher throughout exercise with HFO, even though FIO_2 was adjusted for LFO (Fig 2). Only five patients were able to complete both 12-min exercise protocols; the others had to stop before 12 min due to dyspnea ($n = 5$) with leg discomfort ($n = 3$). Patients were able to exercise longer with HFO compared to LFO (10.0 ± 2.4 min vs 8.2 ± 4.3 min, $p < 0.05$), having less dyspnea ($p = 0.03$, treatment effect two-factor analysis of variance) [Fig 3], at a lower mean arterial pressure and a trend for a lower heart rate (Fig 4). There was no difference in \dot{V}_E , V_T , and WOB in both arms of the study ($p = 0.29$, 0.33 , and 0.18 , respectively); however, RR, RR/V_T , and T_I/T_{TOT} were all lower with HFO compared to LFO ($p = 0.01$, 0.008 , and 0.046 , respectively) [Fig 5]. The same was not observed in the pressure-time

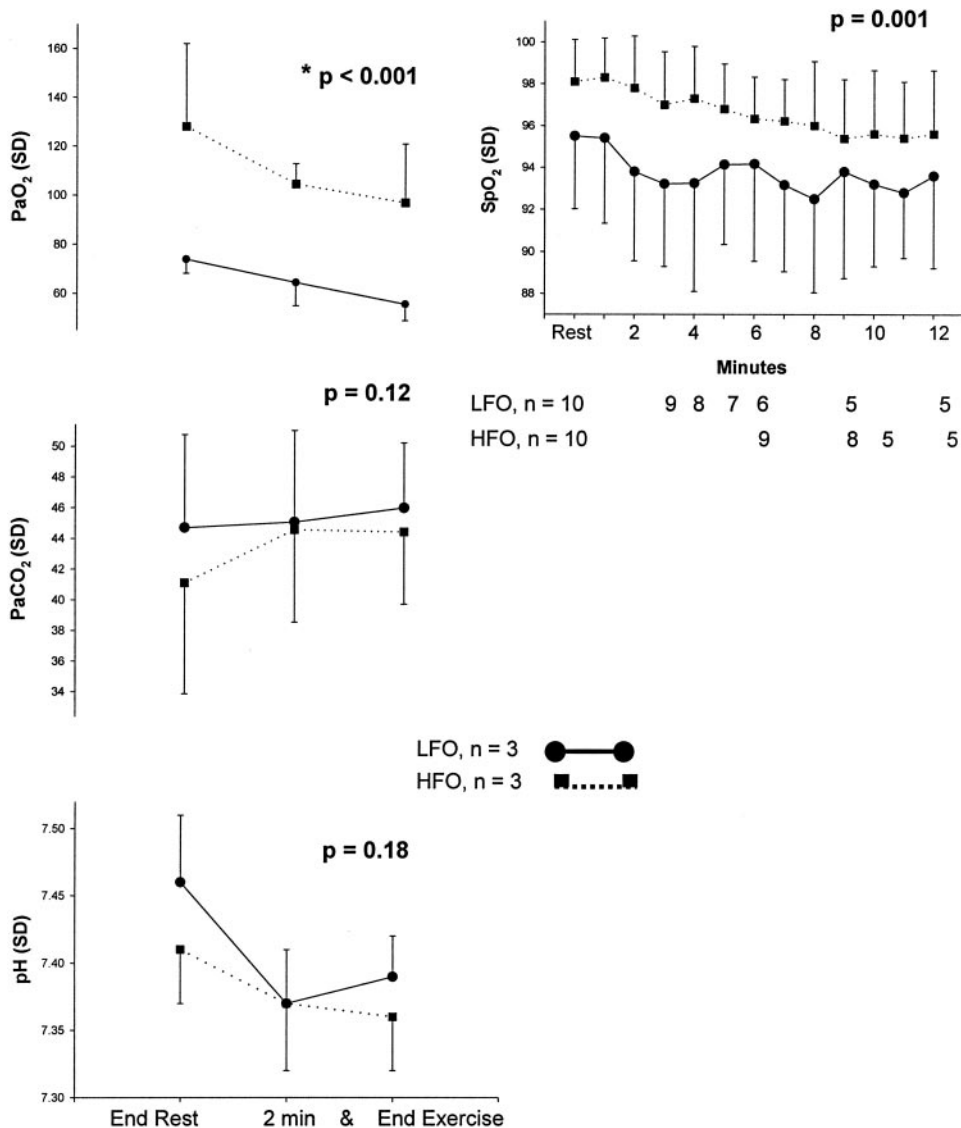


FIGURE 2. Gas exchange variables during rest and exercise. Oxygenation as reflected in PaO₂ (n = 3) and arterial oxygen saturation (SpO₂) (n = 10) was better with HFO delivery throughout the protocol. *Statistical analysis reflects treatment effect, *ie*, Vapotherm HFO vs LFO and not time effect.

product ($p = 0.98$), change in esophageal pressure ($p = 0.73$), and pressure generated during the first 100 ms of a breath ($p = 0.82$).

DISCUSSION

In this study, delivering warm, humidified HFO improved exercise performance in a group of patients with severe COPD. We observed an improvement in oxygenation with HFO at rest that was maintained during exercise despite similar-to-lower FIO₂ compared to LFO delivery. More important, patients were less dyspneic and had lower arterial pressure despite exercising longer. A favorable change in breathing pattern could also be identified

accompanying the gain in endurance during exercise while receiving HFO but not at rest.

The observed improvement in exercise and reduced dyspnea while receiving HFO compared to LFO is likely related to the increased oxygenation. Three possible mechanisms could account for the higher oxygenation at high flows, the first being less entrainment of ambient air, the second due to reduction of dead space, and the third related to attenuation of the ventilatory requirement caused by a combination of a decrease in oxygen cost of breathing and metabolic unloading (decreased lactate production). The design of the study does not allow to quantitate the contribution of each aforementioned factor on oxygenation; however, patient

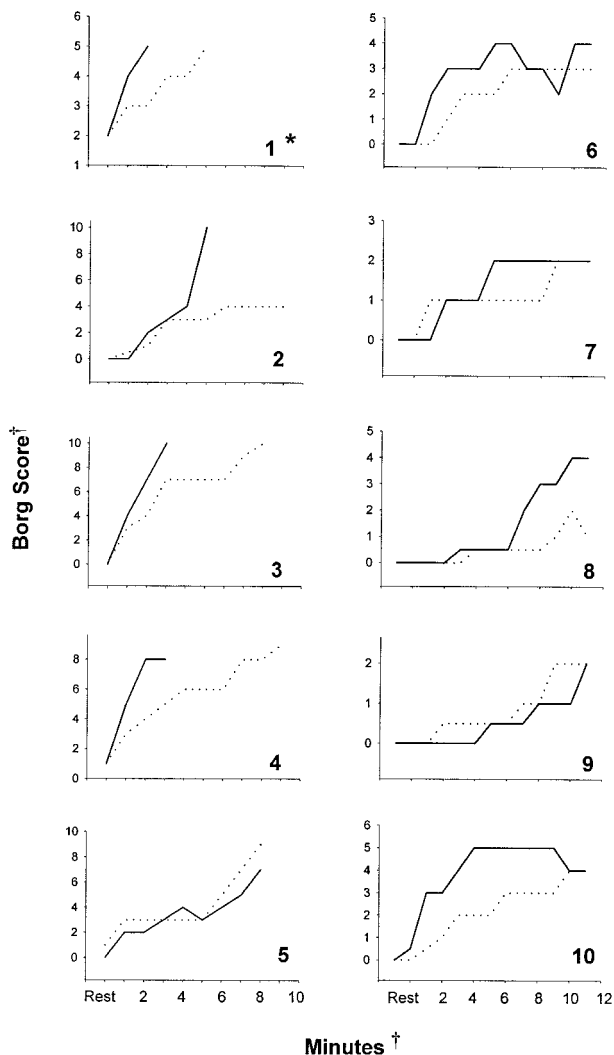


FIGURE 3. Dyspnea scores of individual patients at rest and during exercise. Solid lines indicate LFO; dashed lines indicate HFO. *Patient numbers are shown. †Borg scores and time scales are different between patients 1 to 5 vs patients 6 to 10.

set up (Fig 1, top, A) would suggest that less air entrainment is likely the predominant factor in improving oxygenation. Because Vapotherm HFO was not delivered via nasal cannula in this protocol, one would not expect that high flows significantly reduce dead space when applied at the end of the mouthpiece distal to the flow transducer. However, it is likely that by administering HFO via nasal cannula there will be an added ventilatory and gas exchange benefit beyond that of air entrainment. Tjep and Barnett⁸ measured the FI_{O_2} attainable by a non-breather mask vs high flows (10 to 30 L/min) delivered via nasal cannula and traced flow delivery in an upper airway model using ultrasonic flow studies recorded on digital video. They showed higher attainable FI_{O_2} using the nasal cannula delivery system

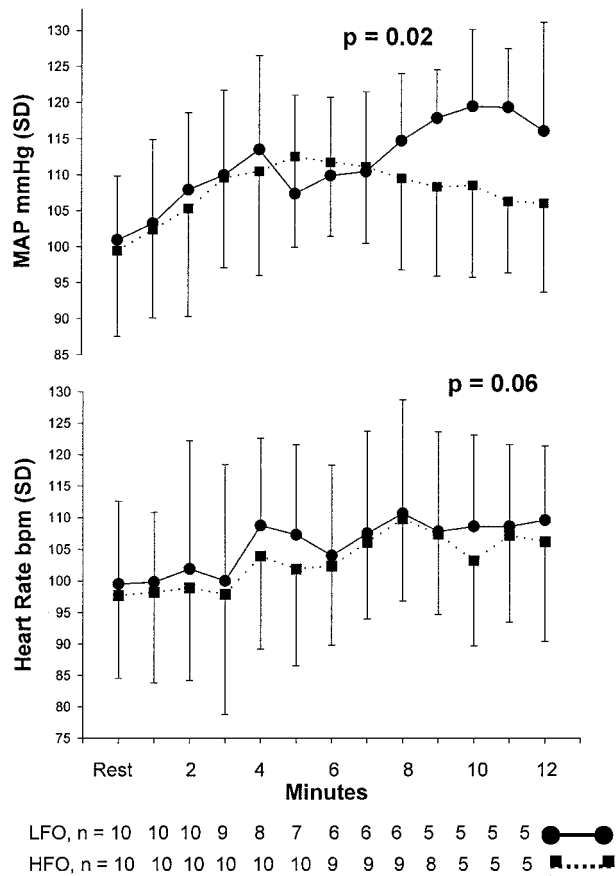


FIGURE 4. Patients had lower BP while exercising receiving HFO. Statistical analyses reflect treatment effect, *ie*, HFO vs LFO and not time effect. MAP = mean arterial pressure; bpm = beats per minute.

but not the nonbreather mask because of upper airway washout; hence, high-flow nasal cannula delivery transformed the upper airway into an oxygen reservoir and reduced dead space in that model. This mechanism is similar to that of transtracheal airway insufflation, which despite being location and flow dependent,^{9,10} was found to be equivalent to HFO delivery via nasal cannula in reducing dyspnea and increasing exercise tolerance.¹¹ Regarding the effects of HFO on respiratory unloading and decreasing ventilatory demands, at least at rest, it is less likely that these factors had a major impact on oxygenation in our patients. First, there was a dramatic 75% increase in PaO_2 while receiving HFO at rest, despite comparable dyspnea and ventilatory parameters to LFO; and second, the WOB was not different between the two delivery systems during the exercise protocol, suggesting that metabolic and ventilatory changes are not the main factors responsible for the hyperoxia.

The ventilatory changes, greater endurance, and lower dyspnea during exercise while receiving HFO

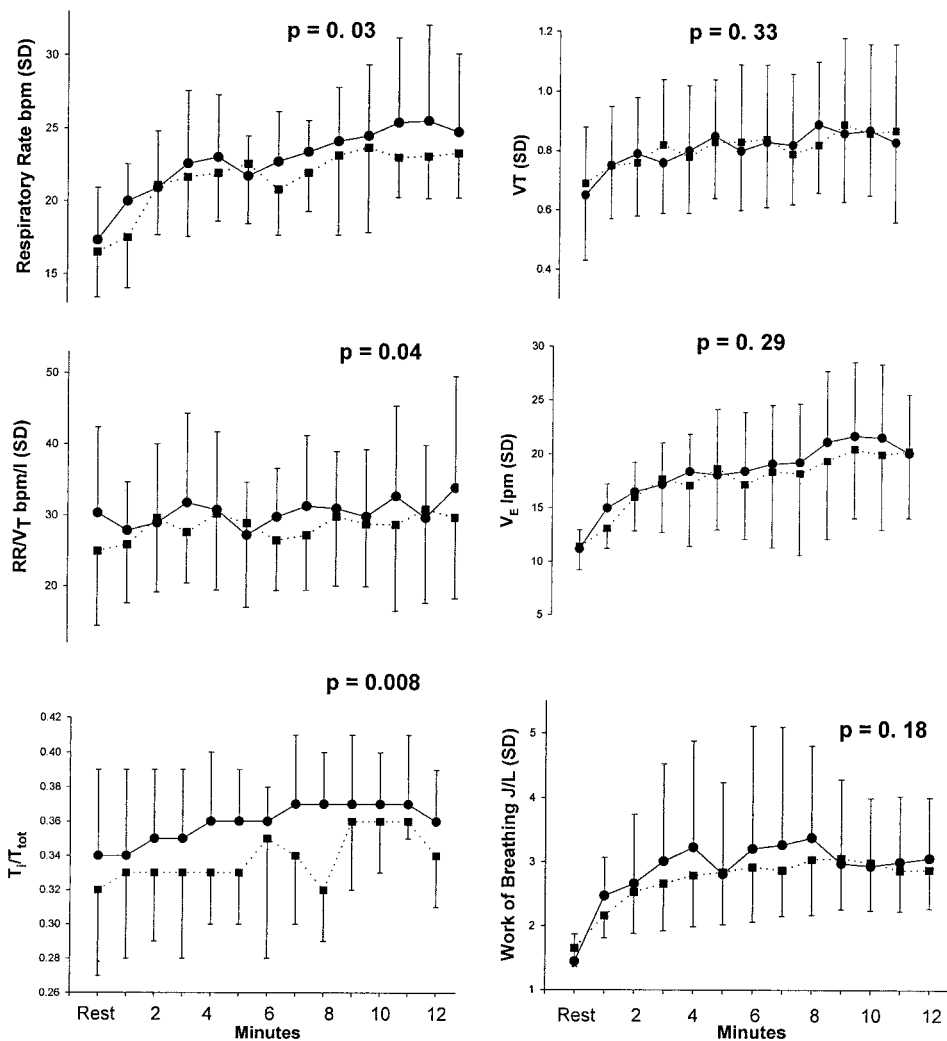


FIGURE 5. Selected ventilatory parameters during rest and exercise. Breathing pattern, but not \dot{V}_E , V_T , and WOB, was better on HFO while exercising. Solid lines indicate LFO; dotted lines indicate HFO. For these represented parameters the starting n was either 9 or 10 for each arm of the protocol due to partial loss of data for 2 patients. Statistical analyses reflect treatment effect, *ie*, high-flow vs low-flow and not time effect. bpm/l = beats per minute per liter; see Figures 1 and 4 for expansion of abbreviations.

are consistent with the effects of hyperoxia on exercise performance in patients with COPD. Oxygen has been shown to improve exercise tolerance in a dose-dependent fashion,¹² and O'Donnell and colleagues¹³ reported similar findings in a double-blind crossover study in patients with severe COPD exercising on 60% F_{IO_2} vs room air. The reduction in dyspnea and ventilation has been also shown to occur at rest with hyperoxia,¹⁴ a finding that was not duplicated in this study because our patients were never hypoxemic during the protocol. This improvement in exercise capacity and reduced dyspnea with hyperoxia has been attributed to a decrease in ventilatory demands, decrease in dynamic end-expiratory volumes, and alteration in respiratory

muscle recruitment.^{13,15,16} The fact that our patients exercised while receiving oxygen probably has attenuated the difference between HFO and LFO on some of the measured parameters, hence the trend for a reduction in \dot{V}_E or WOB. Nevertheless, although we did not measure inspiratory capacity during exercise, breathing patterns improved (decreased RR, RR/VT, and T_i/T_{TOT}) on HFO consistent with a reduction in end-expiratory volumes that accompanies dyspnea relief, with evidence of a moderate correlation between T_i/T_{TOT} and dyspnea scores ($r = 0.5$, $p < 0.01$).

There are other mechanisms independent of oxygenation that are likely to contribute to the observed differences between HFO and LFO, some of which

could be more functional using nasal cannula for Vapotherm HFO delivery. Firstly, warm humidification of the upper airway might have multiple physiologic benefits, resulting not only in more comfort but also improved airway function. Warm humidification conditioned to core temperature and 100% relative humidity maintains the rheology of airway secretions, maximizes mucociliary clearance, and may prevent inflammatory reactions, thus improving on airway function.¹⁷ Moreover, nasal breathing of humidified air inhibits the nasopulmonary bronchoconstrictor reflex, thus preventing any increase in airway resistance that could be triggered by cold and dry air.^{18–20} Secondly, high-flow via nasal cannula can generate positive pressure within the upper airways, counterbalancing the intrinsic positive end-expiratory pressure in patients with significant air trapping and hyperinflation, such as ours (Table 1). The extent of unloading will obviously depend on the nasal and respiratory mechanics as well as the set flow rates. As expected, we have observed an incremental rise in tracheal pressures in a normal subject who received HFO at different flows (Fig 6).

This study is not without limitations. The number of patients was relatively small, and they were not randomized for the sequence of the exercise. LFO was always first during the protocol; hence, some of the results may have been related to a learning effect. Moreover, besides improvement in oxygenation, this study does not offer insight into the mechanisms of the effect of HFO. Although we studied only 10 patients, we were able to show differences in our primary outcome, *ie*, oxygenation and dyspnea, coupled with an improvement in breathing pattern. By adding more patients, we could have perhaps accentuated those differences without unveiling new findings. Regarding the lack of randomization for oxygen delivery and learning effect, first, no study has demonstrated such an improvement in so little time of rest with only one short training session in such patients. However, it takes prolonged rehabilitation and significant training (*eg*, three 45-min sessions per week for up to 6 weeks) to show a modest improvement in respiratory parameters in patients with severe COPD.²¹ Second, this concern would have been more valid if patients started with HFO first. In our patients, the extent of dynamic hyperinflation during the first round of exercise would have negatively affected their mechanical efficiency¹³ during the second round on exercise with HFO. Therefore, it is more than likely that the observed differences between the two delivery systems have been lessened by starting LFO always first.

In conclusion, patients with severe COPD felt less dyspneic and exercised longer while receiving hu-

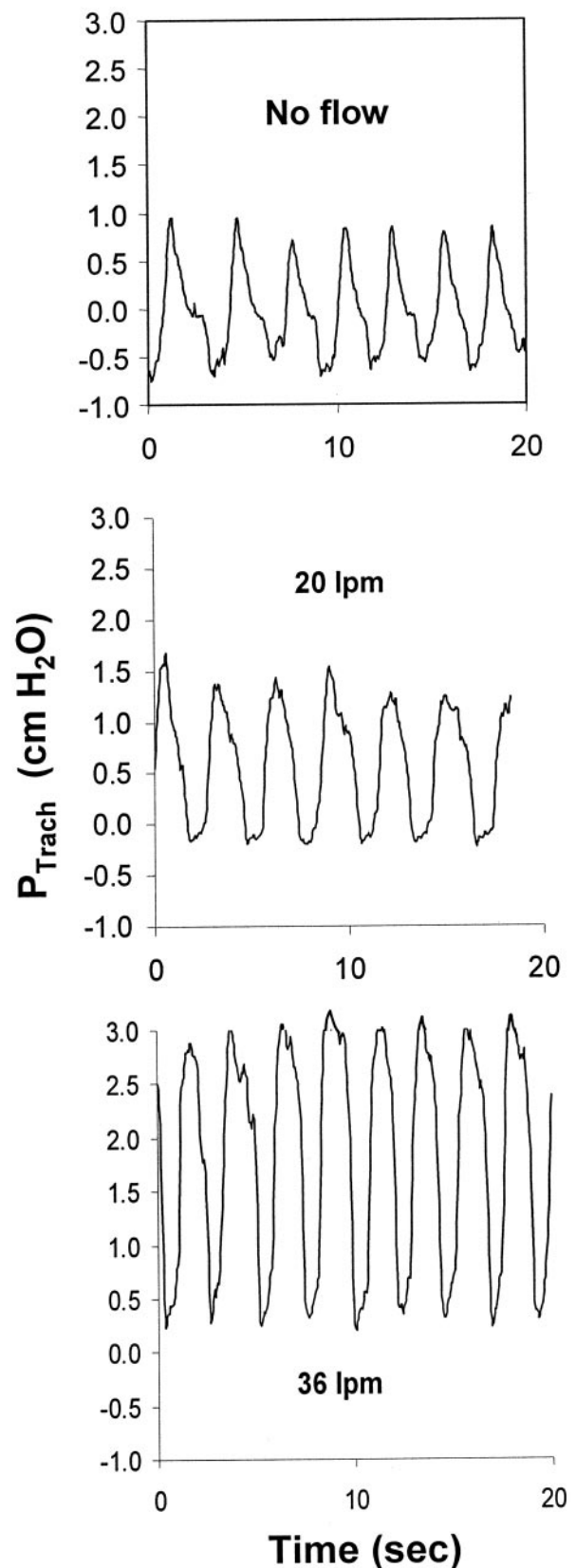


FIGURE 6. Airway tracheal pressure (P_{Trach}) measured in a subject during no flow and two different base flows through Vapotherm device. There is a rise in tracheal airway pressure with increasing Vapotherm HFO. See Figure 1 for expansion of abbreviation.

modified HFO compared to LFO delivery. Despite similar-to-higher F_{IO_2} requirements during LFO delivery, oxygenation was better with HFO even when patients exercised more. Although the difference in oxygenation can explain many of our observations, other mechanisms such as resistive unloading and improved airway function and lung mechanics might be variably involved in enhancing exercise performance and comfort. Noninvasive ventilation and nonrebreather masks have offered some relief to patients with COPD who are challenged by increasing respiratory loads and hypoxemia; however, their use is not universal in part because of side effects and portability. The Vapotherm device might act as an intermediate form of respiratory support falling between traditional oxygen delivery via the nasal cannula and noninvasive ventilation helping patients to cope with their load. It remains to be determined whether the Vapotherm device, or other means to deliver user-friendly ventilatory support, will have an impact on various clinical outcomes.

REFERENCES

- 1 Gallagher CG. Exercise and chronic obstructive pulmonary disease. *Med Clin North Am* 1990; 74:619–641
- 2 Skeletal muscle dysfunction in chronic obstructive pulmonary disease: a statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999; 159:S1–S40
- 3 Scanlan CL, Heuer A. *Medical gas therapy*. 8th ed. St Louis, MO: Egan's fundamentals of respiratory care, 1999; 737–770
- 4 Kacmarek RM. Complications of tracheal gas insufflation. *Respir Care* 2001; 46:167–176
- 5 Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO workshop report; updated 2003. Bethesda, MD: National Institutes of Health, 2003
- 6 Milic-Emili J, Mead J, Turner JM, et al. Improved technique for estimating pleural pressure from esophageal balloons. *J Appl Physiol* 1964; 19:207–211
- 7 Littell RC, Pendergast J, Natarajan R. Modelling covariance structure in the analysis of repeated measures data. *Stat Med* 2000; 19:1793–1819
- 8 Tiep B, Barnett M. High flow nasal vs. high flow mask oxygen delivery: tracheal gas concentrations through a head extension airway model [abstract]. *Respir Care* 2002; 47:1079
- 9 Hurewitz AN, Bergofsky EH, Vomero E. Airway insufflation: increasing flow rates progressively reduce dead space in respiratory failure. *Am Rev Respir Dis* 1991; 144:1229–1233
- 10 Ravenscraft SA, Burke WC, Nahum A, et al. Tracheal gas insufflation augments CO_2 clearance during mechanical ventilation. *Am Rev Respir Dis* 1993; 148:345–351
- 11 Dewan NA, Bell W. Effect of low flow and high flow oxygen delivery on exercise tolerance and sensation of dyspnea: a study comparing the transtracheal catheter and nasal prongs. *Chest* 1994; 105:1061–1065
- 12 Davidson AC, Leach R, George RJD, et al. Supplemental oxygen and exercise ability in chronic obstructive airways disease. *Thorax* 1988; 43:965–971
- 13 O'Donnell DE, D'Arsigny C, Webb K. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163:892–898
- 14 Alvisi V, Mirkovic T, Nesme P, et al. Acute effects of hyperoxia on dyspnea in hypoxemia patients with chronic airway obstruction at rest. *Chest* 2003; 123:1038–1046
- 15 Criner GJ, Celli BR. Ventilatory muscle recruitment in exercise with O_2 in obstructed patients with mild hypoxemia. *J Appl Physiol* 1987; 63:195–200
- 16 Pardy RL, Bye PT. Diaphragmatic fatigue in normoxia and hyperoxia. *J Appl Physiol* 1985; 58:738–742
- 17 Williams R, Rankin N, Smith T, et al. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med* 1996; 24:1920–1929
- 18 Fontanari P, Burnet H, Zattara-Hartmann MC, et al. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. *J Appl Physiol* 1996; 81:1739–1743
- 19 Fontanari P, Zattara-Hartmann MC, Burnet H, et al. Nasal eupnoic inhalation of cold, dry air increases airway resistance in asthmatic patients. *Eur Respir J* 1997; 10:2250–2254
- 20 On LS, Boonyongsunchai P, Webb S, et al. Function of pulmonary neuronal M(2) muscarinic receptors in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163:1320–1325
- 21 Casaburi R, Porszasz J, Burns MR, et al. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 155:1541–1551