# Expiratory flow limitation and heliox breathing in resting and exercising COPD patients

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**Abstract**

In 26 stable patients with chronic obstructive pulmonary disease, tidal expiratory flow limitation (TEFL), inspiratory capacity, breathing pattern and dyspnea sensation were assessed during air and heliox (20% $O_2$ in He) breathing at rest and during exercise up to 2/3 maximal work rate. Breathing air, the 13 patients with TEFL at rest remained flow-limited also during exercise, while 7 of the non flow-limited patients became flow-limited; tidal volume increased more in non flow-limited patients, whereas inspiratory capacity decreased in flow-limited and increased in the non flow-limited patients. Heliox did not abolish flow limitation, had no effect on breathing pattern, reduced exercise dynamic hyperinflation in 25% of the flow-limited patients, depending on the degree of the dynamic hyperinflation on air, and lessened dyspnea sensation in all patients. Hence, presence of TEFL has no systematic effects on the respiratory response to heliox, and the heliox-induced decrease of exercise dyspnea is not mainly due to changes in dynamic hyperinflation or TEFL.

## 1. Introduction

In COPD patients, helium-oxygen mixtures (heliox) have been and are still being used on the presumption that if turbulent flow occurs during tidal breathing, airway resistance would decrease, and flow, tidal volume, and inspiratory capacity increase, thus improving the efficiency of the respiratory performance and, as a consequence, the working capacity. Results obtained both at rest and during exercise are, however, contradictory.

At rest, a decrease in pulmonary resistance with heliox administration but no effect on dynamic hyperinflation was observed in COPD patients by Grapé et al. (1960), whereas no change in total respiratory resistance but an increase in inspiratory capacity was found by Wouters et al. (1992) and Swida et al. (1985), respectively. These discrepancies could be related to the occurrence of expiratory flow limitation with its different mechanisms. In fact, Meadows et al. (4) found that only half of their COPD patients performing an expiratory forced vital capacity maneuver, exhibited an increase in maximal expiratory flows with heliox. Three recent studies have failed, however, to show any effect (Pecchiari et al., 2004; Palange et al., 2004; Eves et al., 2006). During muscular exercise, heliox administration has been found to be beneficial in COPD patients in terms of symptoms and exercise capacity (Palange et al., 2004; Laude et al., 2006; O'Donnell et al., 2007). This favorable effect of heliox has been attributed to increased maximal ventilation and tidal volume at peak exercise, and reduction in dynamic hyperinflation at iso-time (Palange et al., 2004; Eves et al., 2006). In contrast, no significant effects were found by other studies (Raimondi et al., 1970; Bradley et al., 1980; Oelberg et al., 1998; Johnson et al., 2002).

These contrasting respiratory responses could reflect differences among studies in the preponderance of flow-limited COPD patients, and nature of the expiratory flow-limitation, i.e the viscous or the density dependent wave speed mechanism. Since heliox does not lessen dynamic hyperinflation of resting flow-limited patients (Pecchiari et al., 2004), its effects should be minor also during exercise if flow-limitation were still due to the viscous, density independent mechanism. In non flow-limited patients, however, heliox could improve the respiratory performance by lessening airway resistance, increasing maximal flows, and lowering end-expiratory lung volume. Indeed, normal subjects increase pulmonary ventilation and inspiratory capacity with heliox at higher work loads, when high flows are achieved and functional residual capacity increases while breathing air (Babb, 1997a; 1997b; McClaran et al., 1999). The present study has, therefore, compared the ventilatory response to heliox administration in expiratory flow-limited or non flow-limited COPD patients both at rest and during normal, non-fatiguing physical activities.

## 2. Methods

Twenty-six, stable COPD patients were studied. Patients had no cardiovascular and other pulmonary diseases, nor upper respiratory tract infections during the previous month, and none was being treated with oral $\beta_2$-agonists, theophylline or systemic corticosteroids, or had received inhaled short-acting $\beta_2$-agonistic or anticholinergic drugs for 8 h or long-acting $\beta_2$-agonists for 24 h before the study. The study was approved by the local Ethics Committee and by CCT (ISRCTN15098442). Informed consent was obtained from all patients.

Pulmonary function was assessed with standard methods and procedures (Quanier, 1983), using a body plethysmograph (Elite Series; MedGraphics, Saint Paul, MN) and reference values from Quanier (1983). Predicted values of inspiratory capacity (IC) were computed as difference between predicted total lung (TLC) and functional residual capacity (FRC). Arterial oxygen and carbon dioxide partial pressure and pH were measured with ABL 700 (Radiometer, Copenhagen, Denmark). Chronic dyspnea was evaluated using the modified Medical Research Council (MRC) scale (Eltayara et al., 1996).

In preliminary sessions, the patients, breathing ambient air, performed an incremental exercise test on a cycle ergometer (LODE; Medical Technology, Groningen Holland) to assess maximal oxygen consumption ($\dot{V}O_2$peak) and work rate ($\dot{W}$max). $\dot{V}O_2$ was measured with Vmax 29c (Sensor Medics, Yorba Linda, CA), using reference values from Wasserman et al. (1986).

Patients who felt uncomfortable with the breathing circuit or exercising at 2/3 $\dot{W}$max fatiguing, were excluded from the study.

In a subsequent session, the patients were investigated in the afternoon while breathing air and 10 min after equilibration with heliox (20% $O_2$-80% He), both at rest and exercising at 1/3 and 2/3 $\dot{W}$max for 6-8 min at each work level, measurements being taken when a quasi-steady breathing pattern had established. The test sequence was randomized. About one hour elapsed between air and heliox tests, patients being kept unaware of the gas mixture breathed. The equipment has been described previously (Pecchiari et al., 2004). The pneumotachograph, calibrated with air or heliox, was linear over the experimental flow range. The equipment resistance ($cmH_2O \cdot s \cdot L^{-1}$) was $0.72+0.07\dot{V}$ on air and $0.63+0.03\dot{V}$ on heliox. The digitized flow signal was analyzed (LabVIEW; National Instruments, Austin, TX) to obtain tidal volume ($V_T$), inspiratory ($T_I$) and expiratory duration ($T_E$), and pulmonary ventilation ($\dot{V}_I$), besides IC. The electrocardiogram (Cardio Soft; Sensor Medics, Yorba Linda, CA) and oxygen saturation (8500M-Pulseoximeter; Nonin Medical Inc., Plymouth, MN) were continuously recorded, the latter being >90%. Perceived breathlessness was assessed using the Borg 10-point scale.

Both at rest and during exercise while breathing room air or heliox, 4-6 negative expiratory pressure (NEP) tests were performed, followed by maximal inspirations to assess IC, a reliable and commonly used procedure (Yan et al., 1997; Diaz et al., 2000; Dolmage and Goldstein, 2002). Patients were classified as non flow-limited if the expiratory flow with NEP increased over the entire control $V_T$.

Data, presented as mean ± SD, were analyzed using SPSS 11.5 (SPSS Inc., Chicago, IL). Significance of changes under various conditions was assessed using two-way ANOVA, with Bonferroni correction when required. Correlation between variables was evaluated from Spearman's coefficient ($r_s$), and linear regression analysis. Statistical significance was taken at $P \leq 0.05$.

**3. Results**

Table 1 shows the anthropometric characteristics and baseline lung function data of patients with or without tidal expiratory flow-limitation (TEFL) at rest. The anthropometric characteristics were similar in both groups. Flow-limited patients exhibited greater respiratory resistance, with significantly lower PEF, $FEV_1$, and $FEV_1$/FVC %pred., and were relatively hyperinflated, with significantly greater FRC and lower IC and FVC %pred.. No significant differences occurred between patients with or without TEFL in breathing pattern, arterial blood gasses and pH, which were in the normal range (Table 2).

MRC score was similar in both groups, and correlated with IC and $FEV_1$/ FVC %pred.; presence of TEFL correlated with several variables, the strongest correlation being with IC %pred., as for MRC score (Table 3). With stepwise regression analysis, IC was selected as the only significant predictor of TEFL.

*3.1 Effects of exercise*

In flow-limited and non flow-limited patients at rest, $\dot{W}$max averaged 91±22 and 112±36 watt, respectively; corresponding values of $\dot{V}O_2$peak, %pred. were 66±14 and 80±16% (P=0.03).

While breathing air, patients with TEFL at rest remained flow-limited also during exercise. Of the 13 non flow-limited patients at rest, 4 and 7 became flow-limited at the lower and higher work level, respectively. The changes of breath timing never differed significantly between patients with and without TEFL, whereas at 2/3 $\dot{W}$max, $V_T$, mean expiratory flow, and $\dot{V}_I$ changes became significantly larger in non flow-limited patients (Table 4).

While breathing heliox, the effects of exercise were qualitatively similar to those observed while breathing air both in patients with and without TEFL: the changes of breath timing never differed significantly between these patients, whereas at 2/3 $\dot{W}$max, those of $V_T$ and $\dot{V}_I$ became significantly larger in non flow-limited patients (Table 5).

At both exercise levels, IC decreased in flow-limited but increased in non flow-limited patients both during air (Table 4) and heliox breathing (Table 5). When end-expiratory (EELV) and end-inspiratory volume (EILV) were expressed as percent TLC, it appeared that with increasing the work rate the flow-limited patients were using most of their IC, in spite of smaller $V_T$'s than non flow-limited patients, independent of the mixture breathed (Fig. 1, upper and middle panels).

Dyspnea was essentially absent at rest, but present during exercise, becoming significantly greater in flow-limited patients at the higher work level both on air (Table 4) and heliox (Table 5).

*3.2 Heliox vs air breathing*

In no instance did heliox abolish TEFL. Furthermore, shifting from air to heliox breathing had no significant effects on the breathing pattern and IC, both at rest and during exercise (Table 6). Indeed, when data from both flow-limited and non flow-limited patients obtained at rest or at a given exercise level were pooled, the operating lung volumes were independent of the mixture breathed (Fig. 1, lower panel).

Though not influential on the overall behavior, exercise IC increased significantly with heliox in 3 of the 13 patients flow-limited at rest (ΔIC=0.15±0.03 L), in 2 of the 7 patients who became flow-limited with exercise (ΔIC=0.17±0.05 L), and in 1 of the 6 patients who were always non flow-limited (ΔIC=0.22±0.04 L). On the other hand, IC decreased significantly in one non flow-limited patient (ΔIC=-0.22±0.03 L). It should be noted that the breath-by-breath variation of EELV averaged 0.09±0.06 L (range: 0.05-0.12 L), independent of TEFL and work rate.

Heliox lessened exercise dyspnea in both groups of patients, the reduction being significant only at 2/3 $\dot{W}$ max (Table 6). At this work rate, the changes in Borg score were -2±1.4, -2.3±2.9, and –1.2±0.8 in 15 flow-limited patients who did not change IC with heliox, 5 flow-limited patients who increased IC with heliox, and 6 non flow-limited patients, respectively, these values being not significantly different (P=0.479).

## 4. Discussion

This is the first study that addresses the role of tidal expiratory flow limitation in the response to exercise and heliox breathing of mild to moderate COPD patients. Its main finding is that the ventilatory response to non-fatiguing exercises differs between expiratory flow-limited and non flow-limited patients, whereas heliox has no systematic effects on breathing pattern and dynamic hyperinflation independent of TEFL, but lessens exercise dyspnea.

Because of the aim of the study, consecutive expiratory flow-limited and non flow-limited patients were enrolled in the same number, eliminating those patients who felt breathing through the mouthpiece uncomfortable and/or those who were fatiguing. Although the present patients might not be, therefore, a typical sample of the COPD population, both the differences between flow-limited and non flow-limited patients at rest and the dependencies of MRC score (Tables 1 and 3) are in agreement with previous observations made on a larger number of unselected COPD patients (Pecchiari et al., 2004; Diaz et al., 2000; 2001). The present results also show that IC, % pred. is the only significant predictor of the presence of TEFL at rest and/or during exercise (Table 3), and with the caution due to the small number of patients, individual data suggest that a resting value of IC >80% would ensure a >90% probability that a patient remains non flow-limited at least up to 2/3 $\dot{W}$ max.

While breathing ambient air at rest, the breathing pattern was independent of TEFL (Table 2), in line with previous observations (Pecchiari et al., 2004; Diaz et al., 2001). During exercise, only $V_T$ increased more in non flow-limited patients, accounting for the greater changes in $\dot{V}_I$ (Table 4). These differences were in part due to the work rate being expressed relative to individual $\dot{W}$ max. However, when the work rate was expressed in absolute terms, the slope of the $\Delta V_T$-$\dot{W}$ relationship was still significantly lower in flow-limited than non flow-limited patients (6.4±0.6 vs 8.7±0.6 ml/watt; P<0.016), indicating that exercising patients with TEFL do increase their tidal volume less than non flow-limited patients independent of work rate, likely because of the concomitant dynamic hyperinflation. IC increased in non flow-limited patients, as it occurs in normal subjects (Babb, 1997a; 1997b; McClaran et al., 1999), but decreased in flow-limited patients

(Table 4), accounting for the smaller $V_T$'s attained by these patients, the relative increase of EILV being similar in both groups of patients (Fig. 1). The increase in operating lung volumes is in fact the main mechanism whereby in flow-limited patients expiratory flow can be increased, $T_E$ shortened and yet $V_T$ augmented, allowing for higher $\dot{V}_I$. An additional mechanism is probably represented by the fall in airway resistance with exercise (Raimondi et al., 1970; Warren et al., 1984). In contrast, in the non flow-limited patients about 25% of the increase in $V_T$ was due to the fall of EELV (Fig. 1).

While breathing heliox, the changes of breathing pattern and IC with exercise were qualitatively similar to those observed while breathing air in the flow-limited and non flow-limited patients, respectively (Table 5). Indeed, heliox had no effect on the breathing pattern at rest or during exercise (Table 6). While heliox can increase exercise ventilation in subjects with normal pulmonary function and TEFL during exercise, though not assessed with the NEP technique (McClaran et al., 1999; Babb, 2001), no such an effect is seen in COPD patients when comparisons are made using present and published data (Raimondi et al., 1970; Bradley et al., 1980; Babb, 1997b; Palange et al., 2004) obtained under the same conditions, including time from the onset of exercise. Furthermore, the present results indicate that absence of changes in the breathing pattern with heliox is independent of TEFL and IC changes (Table 6).

At rest, heliox had no effect on the end-expiratory lung volume, independent of TEFL (Table 6 and Fig. 1). Similar results have been obtained in a previous study (Pecchiari et al., 2004) and in resting COPD patients in whom TEFL was not assessed (Palange et al., 2004; Eves et al., 2006). Given the prevalence of TEFL in COPD patients (Koulouris et al., 1997; Diaz et al., 2000; Pecchiari et al., 2004), the results of the latter studies also indicate that heliox has no effect on resting IC independent of TEFL. Because during quite breathing, like passive expiration, heliox can increase maximal expiratory flows and reduce IC only if the flow-limiting segment were located in the central airways (Brighenti et al., 2007), all these results indicate that at rest TEFL is due usually to mechanical alterations of peripheral airways. It should be, therefore, expected that in patients who are flow-limited at rest, heliox would not affect IC during exercise, as generally seen in the present study, as well as in normal subjects who become flow-limited during sub-maximal exercise (Babb, 2001).

At variance with the present results obtained during non-fatiguing exercises, heliox has been shown to increase mean IC of exercising COPD patients at the time of exhaustion during room air breathing without affecting the breathing pattern (Palange et al., 2004; Eves et al., 2006). This discrepancy is not accounted for by differences in the severity of the disease, as assessed from common pulmonary function tests, or relative intensity of the exercise, but it could depend on the conditions in which measurements were performed causing different degrees of dynamic hyperinflation and location of the flow-limiting segment. Indeed, heliox has no effect in non flow-limited patients in whom exercise IC increases during air breathing (Tables 5 and 6, and Fig. 1 and 2), as it happens in normal non flow-limited subjects (Babb, 1997a; 1997b; McClaran et al., 1999), while in the absence of $V_T$ and $T_E$ changes (Table 6; Palange et al., 2004; Eves et al., 2006), the effect of heliox on IC must reflect the location of the flow-limiting segment. In patients with TEFL, an increase of IC can occur only if the flow-limiting segment moves with exercise from the peripheral to the central airways, thus allowing for increased maximal expiratory flows, as it happened in some patients flow-limited at rest, and in the majority of those studied by Palange et al. (2004) and Eves et al. (2006). This shift should in turn depend primarily on the increase in EELV which takes place during exercise while breathing air. Indeed, *a)* a significant negative correlation is observed in the present flow-limited patients between the decrease in IC with exercise while breathing ambient air and the subsequent changes caused by heliox (Fig. 2); and *b)* the decrease in IC during air breathing is substantially greater in Palange (-0.27 L) and Eves patients (-0.84 L, 9.3%TLC) than in the present flow-limited patients (-0.18 L, 2.6%TLC).

The present results do not allow the identification of the functional characteristics that distinguish the flow-limited COPD patients who, during exercise on air, increase their EELV sufficiently to move the choke point from the peripheral to the central airways, thus accounting for the increase in IC while breathing heliox. Indeed, none of the variables measured at rest (Table 1 and 2) differed significantly between the 20 flow-limited patients who did not increase exercise IC on heliox (non-responders) and the 5 flow-limited patients who did so (responders). Based on a model study (Brighenti et al., 2007), it can be predicted that responders are those patients who exhibit, relative to non-responders, a more accentuated decrease in peripheral (RPAW) than total apparent airway resistance (RAPP) with increasing lung volume; in these patients a RPAW/RAPP<1, which implies a substantial density dependent component of RAPP, should be, therefore, reached at EELV levels that still permit adequate exercise VT's, otherwise impracticable or too expensive in terms of elastic work for non-responders. If this were the case, differences between responders and non-responders would concern the volume dependence of both peripheral and central airway resistance, as determined by the intrinsic mechanical characteristics of the airways, bronchomotor tone, oedema of airway walls, secretions, and lung recoil. Because of the many factors involved and their complicated interplay, a more complete set of common functional tests at rest and a much larger sample of both responders and non-responders are needed to distinguish between the two types of COPD patients.

Bronchodilators have no effect on lung volumes and breathing pattern in non flow-limited COPD patients (Tantucci et al., 1998; Pecchiari et al., 2004), but increase IC of flow-limited patients, both at rest and during exercise (Tantucci et al., 1998; Pecchiari et al., 2004; O'Donnell et al., 2007). This systematic increase of IC contrasts with the variability of IC changes observed with heliox in flow-limited patients during exercise, further suggesting that, while bronchodilators lower both central and peripheral airway resistance, the effectiveness of heliox administration depends on the central or peripheral location of the flow-limiting segment.

Tolerance of COPD patients to incremental or constant load exercise is either unchanged (Raimondi et al., 1970; Bradley et al., 1980; Oelberg et al., 1998) or substantially increased by heliox administration (Palange et al., 2004; Eves et al., 2006; Laude et al., 2006). In the present patients, an indirect evaluation of this effect would be provided by the changes in the sensation of breathlessness, if the latter becomes a limiting factor of exercise performance (Younes, 1991; Tong et al., 2004; O'Donnell et al., 2007). Indeed, heliox lessened the dyspnea both in the present patients during non-fatiguing exercises (Table 6) and in those who were performing endurance tests (Palange et al., 2004; Eves et al., 2006). However, reduction of dyspnea is not necessarily related to changes of respiratory variables, because in COPD patients heliox has no effect on breathing pattern and may (Palange et al., 2004; Eves et al., 2006) or may not affect dynamic hyperinflation (Table 6), while in normal subjects dyspnea perception is unaffected by heliox, in spite of changes in breathing pattern and end-expiratory lung volume (Babb, 1997a; 1997b; 2001; McClaran et al., 1999). Improved respiratory sensation and exercise performance with heliox could be related to inspiratory work, which can decrease up to 50-60% even at fixed EELV and breathing pattern, depending on the extent of turbulent flow and airway resistance on air (Papamoschou, 1995; Brighenti et al., 2007).

In summary, this study has shown that: a) the breathing pattern, which at rest is similar in patients with and without TEFL, differs between the two groups up to 2/3 maximal oxygen consumption, with greater $V_T$ and $\dot{V}_I$, paralleled by increased IC in non flow-limited patients and decreased IC in flow-limited patients; b) both at rest and during exercise, heliox administration does not prevent TEFL, has no effect on the breathing pattern and lung volumes independent of TEFL, but lessens exercise dyspnea in all patients; and c) the capability of heliox breathing to increase IC during exercise observed in previous studies and in some of the present flow-limited patients, should depend on the amount of the upward shift in operating lung volumes while breathing air and the associated displacement of the flow-limiting segment from the peripheral to the central airways.

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**REFERENCES**

Babb, T.G., 1997a. Ventilation and respiratory mechanics during exercise in younger subjects breathing $CO_2$ or $HeO_2$. Respir. Physiol. 109, 15-28.

Babb, T.G., 1997b. Ventilatory response to exercise in subjects breathing $CO_2$ or $HeO_2$. J. Appl. Physiol. 82, 746-754.

Babb, T.G., 2001. Breathing He-$O_2$ increases ventilation but does not decrease the work of breathing during exercise. Am. J. Respir. Crit. Care Med. 163, 1128-1134.

Bradley, B.L., Forman, J.W., Miller, W.C., 1980. Low-density gas breathing during exercise in chronic obstructive lung disease. Respiration 40, 311-316.

Brighenti, C., Barbini, P., Gnudi, G., Cevenini, M., Pecchiari, M., D'Angelo, E., 2007. Helium-oxygen ventilation in the presence of expiratory flow limitation: a model study. Respir. Physiol. & Neurobiol. 157, 326-334.

Diaz, G., Villafranca, C., Ghezzo, H., Borzone, G., Leiva, A., Milic-Emili, J., Lisboa, C., 2000. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal flow limitation at rest. Eur. Respir. J. 16, 269-275.

Diaz, G., Villafranca, C., Ghezzo, H., Borzone, G., Leiva, A., Milic-Emili, J., Lisboa, C., 2001. Breathing pattern and gas exchange at peak exercise in COPD patients with and without tidal flow limitation at rest. Eur. Respir. J. 17, 1120-1127.

Dolmage, T.E., Goldstein, R.S., 2002. Repeatability of inspiratory capacity during incremental exercise in patients with severe COPD. Chest 121, 708-714.

Eltayara, L., Becklake, M.R., Volta, C.A., Milic-Emili, J., 1996. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 154, 1726-1734.

Eves, N.D., Petersen, S.R., Haykowsky, M.J., Wong, E.Y., Jones, R.L., 2006. Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 174, 763-771.

Grapé, B., Channin, E, Tyler, J.M., 1960. The effect of helium and oxygen mixtures on pulmonary resistances in emphysema. Am. Rev. Respir. Dis. 81, 823-829.

Johnson, J.E., Gavin, D.J., Adams-Dramiga, S., 2002. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. Chest 22, 464-472.

Koulouris, N.G., Dimopoulou, I., Valta, P., Finkelstein, R., Cosio, M.G., Milic-Emili, J., 1997. Detection of expiratory flow limitation during exercise in COPD patients. J. Appl. Physiol. 82, 723-731.

Laude, E.A., Duffy, N.C., Baveystock, C., Dougill, B., Campbell, M.J., Lawson, R., Jones, P.W., Calverley, P.M., 2006. The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 173, 865-870.

McClaran, S.R., Wetter, T.J., Pegelow, D.F., Dempsey, J.A., 1999. Role of expiratory flow limitation in determining lung volumes and ventilation during exercise. J. Appl. Physiol. 86, 1357-1366.

Meadows, J.A.III, Rodarte, J.R., Hyatt, R.E., 1980. Density dependence of maximal expiratory flow in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis.121, 47-53.

O'Donnell, D., Banzett, R.B., Carrieri-Kohlman, V., Casaburi, R., Davenport, P.W., Gandevia, S.C., Gelb, A.F., Mahler, D.A., Webb, K.A., 2007. Pathophysiology of dyspnea in chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. 4, 145-168.

Oelberg, D.A., Kacmarek, R.M., Pappagianopoulos, P.P., Ginnis, L.C., Systrom, D.M., 1998. Ventilatory and cardiovascular responses to inspired He-$O_2$ during exercise in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 158, 1876-1882.

Palange, P., Valli, G., Onorati, P., Antonucci, R., Paoletti, P., Rosato, A., Manfredi, F., Serra, P., 2004. Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. J. Appl. Physiol. 97, 1637-1642.

Papamoschou, D., 1995. Theoretical validation of the respiratory benefits of helium-oxygen mixtures. Respir. Physiol. 99, 183-190.

Pecchiari, M., Pelucchi, A., D'Angelo, Em., Foresi, A., Milic-Emili, J., D'Angelo, E., 2004. Effect of heliox breathing on dynamic hyperinflation in COPD patients. Chest 125, 2075-2082.

Quanier, P.J., 1983. Standardized lung fuction testing. Report of the working party: standardization of lung function tests. Bull. Eur. Physiopathol. Respir. 19 (suppl. 5), 1-95.

Raimondi, A.C., Edwards, H.T., Denison, D.M., Leaver, D.G., Spencer, R.G., Siddorn, J.A., 1970. Exercise tolerance breathing a low density gas mixture, 35% oxygen and air in patients with chronic obstructive bronchitis. Clin. Sci. 39, 675-85.

Swidwa, D.M., Montenegro, H.D., Goldman, M.D., Lutchen, K.R., Saidel, G.M., 1985. Helium-oxygen breathing in severe chronic obstructive pulmonary disease. Chest 87, 790-795.

Tantucci, C., Duguet, A., Similowski, T., Zelter, M., Derenne, J-P., Milic-Emili, J., 1998. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. Eur. Respir. J. 12, 799-804.

Tong, T.K., Fu, F.H., Quach, B., Lu, K., 2004. Reduced sensations of intensity of breathlessness enhances maintenance of intense intermittent exercise. Eur. J. Appl. Physiol. 92, 275-284.

Warren, J.B., Jennings, S.J., Clark, T.J., 1984. Effect of adrenergic and vagal blockade on the normal human airway response to exercise. Clin. Sci. 66, 79-85.

Wasserman, K., Hansen, J.E., Sue, D.Y., Whipp, B.J., 1986. Principles of exercise testing and interpretation. Lea & Febiger, Philadelphia.

Wouters, E.F.M., Landser, F.J., Polko, A.H., Visser, B.F., 1992. Impedance measurements during air and helium-oxygen breathing before and after salbutamol in COPD patients. Clin. Exp. Pharmacol. Physiol. 19, 95-101.

Yan, S., Kaminski, D., Sliwinski, P., 1997. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 156, 55-59.

Younes, M., (1991). Determinants of thoracic excursions during exercise. In: Whipp, B.J., Wasserman, K. (Eds.) Exercise: Pulmonary Physiology and Pathophysiology. Marcel Dekker, New York, NY, pp. 49-50.

Table 1 Anthropometric and routine lung function data of COPD patients with and without tidal expiratory flow-limitation at rest

| | TEFL | no TEFL | P |
|---|---|---|---|
| N | 13 | 13 | |
| Age, yr | 69±7 | 65±7 | n.s. |
| Height, cm | 169±8 | 165±10 | n.s. |
| Weight, kg | 75±9 | 72±10 | n.s. |
| BMI, kg·m$^{-2}$ | 26.2±2.3 | 26.4±3.4 | n.s. |
| MRC scale | 2.2±1 | 1.8±1 | n.s. |
| TLC, % pred. | 111±18 | 110±14 | n.s. |
| FRC, % pred. | 158±22 | 135±25 | 0.020 |
| IC, % pred. | 56±19 | 80±22 | 0.001 |
| FVC, % pred. | 75±15 | 86±11 | 0.035 |
| $FEV_1$, % pred. | 49±12 | 64±9 | 0.003 |
| $FEV_1$/FVC % | 51±6 | 59±10 | 0.016 |
| PEF, % pred. | 50±16 | 77±11 | <0.001 |

Values are mean±SD. TEFL: tidal expiratory flow-limitation; N: number of patients; BMI: body mass index; TLC: total lung capacity; FRC: functional residual capacity; IC: inspiratory capacity; FVC: forced vital capacity; $FEV_1$: forced expired volume in one second; PEF: peak expiratory flow.

Table 2 – Breathing pattern and arterial blood gasses and pH in COPD patients with and without tidal expiratory flow-limitation while breathing ambient air at rest

| | TEFL | no TEFL |
|---|---|---|
| N | 13 | 13 |
| $V_T$, L | 0.67±0.25 | 0.76±0.24 |
| $T_I$, s | 1.24±0.23 | 1.40±0.25 |
| $T_E$, s | 2.82±0.33 | 3.11±0.6 |
| $V_T/T_I$, $L \cdot s^{-1}$ | 0.54±0.15 | 0.56±0.2 |
| $V_T/T_E$, $L \cdot s^{-1}$ | 0.24±0.07 | 0.25±0.1 |
| $\dot{V}_I$, $L \cdot min^{-1}$ | 9.8±2.8 | 10.5±3.9 |
| f, $min^{-1}$ | 15.0±2.1 | 13.7±2.5 |
| pHa | 7.40±0.03 | 7.41±0.02 |
| $PaO_2$, mm Hg | 81±9 | 80±5 |
| $PaCO_2$, mm Hg | 40.4±2.9 | 39.8±2.8 |

Values are mean±SD. TEFL: tidal expiratory flow-limitation; N: number of patients; $V_T$: tidal volume; $T_I$ and $T_E$: inspiratory and expiratory duration; $\dot{V}_I$: pulmonary ventilation; f: breathing frequency.

Table 3 – Spearman's correlation coefficients ($r_s$) of chronic dyspnea and tidal expiratory flow-limitation to resting respiratory variables

| | MRC score | | TEFL | |
|---|---|---|---|---|
| | $r_s$ | P | $r_s$ | P |
| IC, % pred. | -0.525 | 0.006 | -0.663 | <0.001 |
| $FEV_1$/FVC, % | -0.401 | 0.042 | -0.507 | 0.008 |
| $FEV_1$, % pred. | | | -0.640 | <0.001 |
| FRC, % pred. | | | 0.501 | 0.009 |

See Table 1 for definition of abbreviations.

Table 4 – Changes of ventilatory pattern and perceived breathlessness while breathing air at two work intensities in COPD patients with and without tidal expiratory flow-limitation

| | 1/3 $\dot{W}$ max | | | 2/3 $\dot{W}$ max | | |
|---|---|---|---|---|---|---|
| | TEFL | no TEFL | P | TEFL | no TEFL | P |
| N | 17 | 9 | | 20 | 6 | |
| ΔVT, L | 0.24±0.15 | 0.38±0.21 | n.s. | 0.40±0.21 | 0.75±0.22 | 0.007 |
| ΔTI, s | -0.31±0.31 | -0.21±0.18 | n.s. | -0.45±0.29 | -0.39±0.23 | n.s. |
| ΔTE, s | -0.89±0.31 | -0.99±0.45 | n.s. | -1.55±0.38 | -1.88±0.51 | n.s. |
| ΔVT/TI, $L \cdot s^{-1}$ | 0.43±0.22 | 0.43±0.11 | n.s. | 0.82±0.38 | 0.84±0.24 | n.s. |
| ΔVT/TE, $L \cdot s^{-1}$ | 0.22±0.08 | 0.31±0.07 | 0.010 | 0.59±0.21 | 0.86±0.15 | 0.003 |
| Δ $\dot{V}$ I, $L \cdot min^{-1}$ | 8.8±3.4 | 11.0±2.4 | n.s. | 20.8±7.7 | 27.1±4.8 | 0.032 |
| Δf, $min^{-1}$ | 5.8±2.7 | 4.7±2.3 | n.s. | 13.9±4.7 | 11.8±3.5 | n.s |
| ΔIC, L | -0.12±0.17 | 0.17±0.21 | 0.001 | -0.23±0.22 | 0.13±0.07 | 0.001 |
| ΔBorg scale | 0.9±1.1 | 0.8±1.1 | n.s. | 5.2±2.2 | 3.9±1.1 | 0.046 |

Values are mean ±SD. $\dot{W}$ : work rate; IC: inspiratory capacity. See Table 2 for definition of abbreviations.

Table 5 – Changes of ventilatory pattern and perceived breathlessness while breathing heliox at two work intensities in COPD patients with and without tidal expiratory flow-limitation

| | 1/3 $\dot{W}$ max | | | 2/3 $\dot{W}$ max | | |
|---|---|---|---|---|---|---|
| | TEFL | no TEFL | P | TEFL | no TEFL | P |
| N | 17 | 9 | | 20 | 6 | |
| ΔVT, L | 0.28±0.13 | 0.41±0.24 | n.s. | 0.42±0.22 | 0.68±0.18 | 0.012 |
| ΔTI, s | -0.28±0.23 | -0.09±0.31 | n.s. | -0.42±0.27 | -0.17±0.44 | n.s. |
| ΔTE, s | -0.85±0.33 | -0.52±0.58 | n.s. | -1.62±0.41 | -1.38±0.33 | n.s. |
| ΔVT/TI, $L \cdot s^{-1}$ | 0.48±0.24 | 0.40±0.23 | n.s. | 0.85±0.38 | 0.72±0.26 | n.s. |
| ΔVT/TE, $L \cdot s^{-1}$ | 0.23±0.10 | 0.28±0.13 | n.s. | 0.64±0.27 | 0.83±0.16 | n.s. |
| Δ $\dot{V}$ I, $L \cdot min^{-1}$ | 9.3±4.2 | 10.2±5.0 | n.s. | 21.3±4.3 | 24.9±1.6 | 0.049 |
| Δf, $min^{-1}$ | 5.6±2.4 | 3.3±3.2 | n.s. | 14.6±5.3 | 9.8±5.5 | n.s |
| ΔIC, L | -0.11±0.19 | 0.14±0.21 | 0.008 | -0.22±0.23 | 0.06±0.18 | 0.01 |
| ΔBorg scale | 0.4±0.9 | 0.5±0.9 | n.s. | 3.2±1.4 | 1.8±0.7 | 0.043 |

Values are mean ±SD. $\dot{W}$ : work rate; IC: inspiratory capacity. See Table 2 for definition of abbreviations.

Table 6 – Changes in ventilatory pattern and perceived breathlessness (Borg scale) shifting from air to heliox breathing at rest, 1/3, and 2/3 maximal work rate in COPD patients with and without tidal expiratory flow-limitation

| | rest | | 1/3 $\dot{W}$ max | | 2/3 $\dot{W}$ max | |
|---|---|---|---|---|---|---|
| | TEFL | no TEFL | TEFL | no TEFL | TEFL | no TEFL |
| N | 13 | 13 | 17 | 9 | 20 | 6 |
| $\Delta V_T$, L | 0.03±0.14 | 0.01±0.18 | 0.02±0.08 | 0.08±0.16 | 0.02±0.07 | 0.02±0.04 |
| $\Delta T_I$, s | -0.01±0.28 | -0.16±0.24 | -0.04±0.08 | -0.03±0.16 | -0.02±0.05 | 0.02±0.07 |
| $\Delta T_E$, s | 0.11±0.40 | -0.28±0.56 | 0.02±0.21 | 0.07±0.49 | -0.02±0.19 | -0.04±0.15 |
| $\Delta V_T/T_I$, $L \cdot s^{-1}$ | 0.04±0.13 | 0.08±0.13 | 0.08±0.14 | 0.08±0.11 | 0.07±0.12 | 0.0±0.1 |
| $\Delta V_T/T_E$, $L \cdot s^{-1}$ | 0.00±0.04 | 0.03±0.07 | 0.01±0.06 | 0.02±0.09 | 0.05±0.16 | 0.05±0.13 |
| $\Delta \dot{V}_I$, $L \cdot min^{-1}$ | 0.3±1.8 | 1.3±2.6 | 0.8±2.4 | 1.1±2.7 | 1.6±3.9 | 1.0±2.4 |
| $\Delta f$, $min^{-1}$ | -0.4±2.5 | 1.4±2.2 | 0.3±1.8 | 0.3±2.2 | 0.7±2.8 | 0.3±1.9 |
| ΔIC, L | 0.07±0.05 | 0.04±0.11 | 0.09±0.10 | 0.01±0.14 | 0.05±0.07 | 0.03±0.14 |
| Δ Borg scale | 0 | 0 | -0.5±1.3 | -0.3±0.9 | -2.1±1.8* | -1.2±0.7* |

Values are mean±SD. $\dot{W}$ : work rate; IC: inspiratory capacity. See Table 2 for definition of abbreviations. *significantly different from air breathing: P=0.002.

**LEGENDS**

Fig. 1. End-expiratory and end-inspiratory lung volumes as a function of work rate in COPD patients who were always expiratory flow-limited (n=13) or non flow-limited (n=6) while breathing ambient air or heliox, and in all COPD patients (n=26) while breathing ambient air or heliox.

Fig. 2. Changes in inspiratory capacity (IC) between heliox and air breathing during exercise as a function of the corresponding changes in IC between rest and exercise while breathing ambient air in COPD patients with (closed symbols) or without tidal expiratory flow-limitation (open symbols). Continuous and dashed lines are linear regression through data pertaining to flow-limited and non flow-limited patients, respectively. Values refer to the regression obtained for the flow-limited patients.

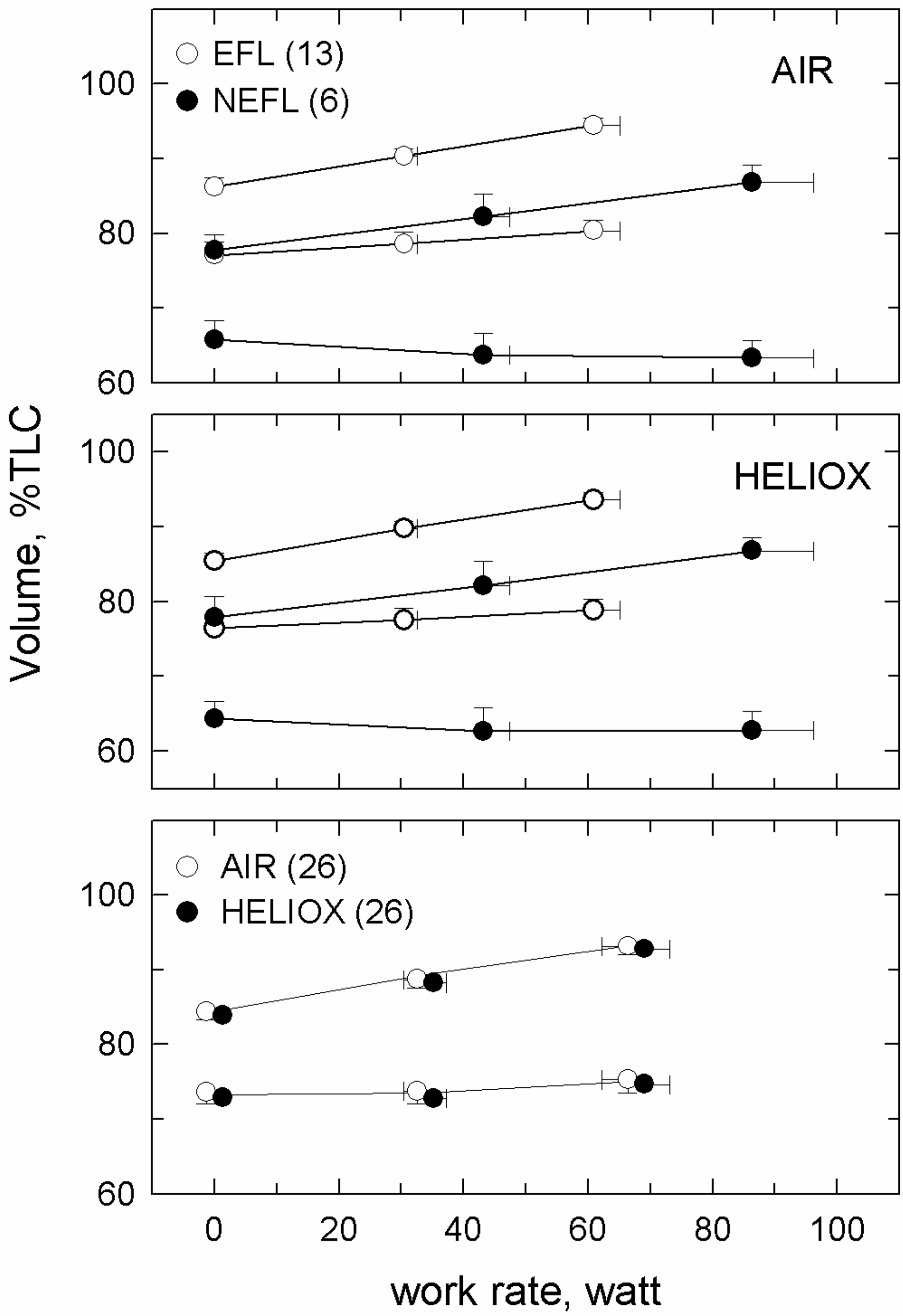
EFL (13)
NEFL (6)
AIR
HELIOX
AIR (26)
HELIOX (26)
Volume, %TLC
work rate, watt
100
80
60
0
20
40
60
80
100

Figure 1

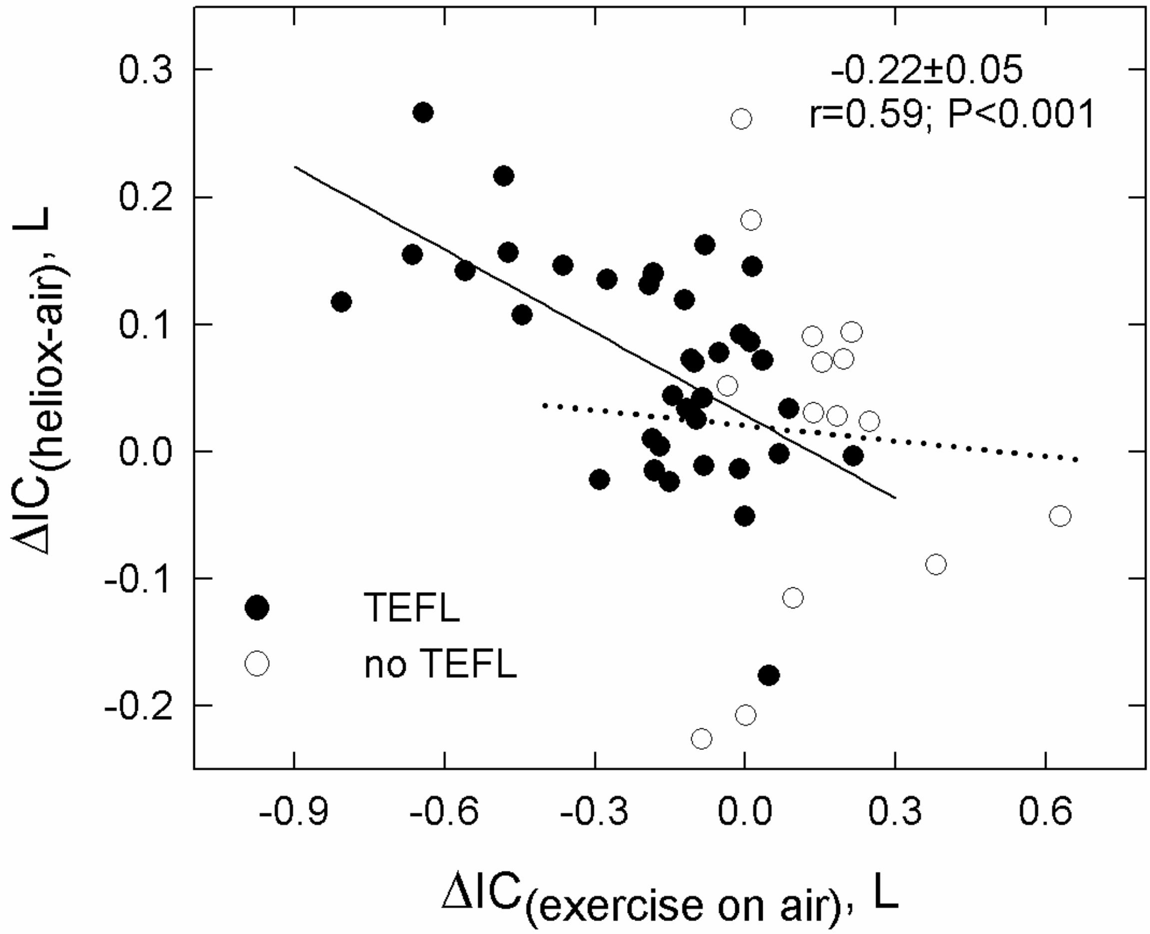
-0.22±0.05
r=0.59; P<0.001
TEFL
no TEFL
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.9
-0.6
-0.3
0.0
0.3
0.6
ΔIC(heliox-air), L
ΔIC(exercise on air), L

Figure 2