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Original article

Relationship Between Expiratory Muscle Dysfunction and Dynamic Hyperinflation in Advanced Chronic Obstructive Pulmonary Disease ☆

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ABSTRACT

Background and objectives: Dynamic hyperinflation and expiratory flow limitation, which are physiologically linked phenomena, play a role in the pathophysiology of dyspnea and have a negative impact on quality of life in patients with chronic obstructive pulmonary disease (COPD). The expiratory muscle dysfunction associated with advanced COPD may be involved in the genesis of dynamic hyperinflation. Our objective was to study the relationship between expiratory muscle dysfunction and dynamic hyperinflation and to analyze their association with dyspnea and quality of life in patients with advanced COPD.

Patients and methods: In 25 patients we measured lung function, exercise capacity (measured by incremental ergometry and the 6-minute walk test), expiratory flow limitation and end-expiratory lung volume (EELV) during exercise, respiratory muscle function, dyspnea, and quality of life (using the St George's Respiratory Questionnaire [SGRQ]).

Results: The patients, whose mean forced expiratory volume in 1 second (FEV1) was 31% of predicted, exhibited a moderate decrease in respiratory muscle strength and resistance to fatigue. Expiratory flow limitation was observed in 19 patients at rest and in 24 patients at 70% of maximal workload (W_{max}). EELV increased from rest to 70% of W_{max} (9% of predicted forced vital capacity). At 70% of W_{max}, EELV correlated inversely with expiratory flow limitation ($\rho=-0.42$), inspiratory ($\rho=-0.43$) and expiratory ($\rho=-0.42$) muscle endurance, and maximal oxygen uptake ($\rho=-0.52$). The increase in EELV from resting to 70% of W_{max} correlated with dyspnea ($\rho=0.53$), and expiratory flow limitation at 70% of W_{max} correlated with the activity score on the SGRQ ($\rho=-0.56$). FEV_1, expiratory muscle endurance and expiratory flow limitation were independent predictors of EELV at 70% W_{max}.

Conclusion: In advanced COPD, decreased resistance to fatigue in expiratory muscles is associated with an increase in dynamic hyperinflation (and less expiratory flow limitation) during exercise, a pattern that in turn correlates with more severe dyspnea and reduced quality of life.

Relación entre disfunción de los músculos espiratorios e hiperinflación dinámica en la EPOC avanzada

RESUMEN

Introducción: La hiperinflación dinámica (HD) y la limitación del flujo espiratorio (LFE) están vinculadas fisiológicamente e intervienen en la fisiopatogenia de la disnea y del deterioro de la calidad de vida en la enfermedad pulmonar obstructiva crónica (EPOC). En la EPOC avanzada existe disfunción de los músculos espiratorios, que podría potenciar el desarrollo de HD. El objetivo del presente trabajo ha sido estudiar la relación entre disfunción muscular espiratoria y grado de HD en la EPOC avanzada, y su asociación con disnea y calidad de vida.

Pacientes y métodos: En 25 pacientes determinamos la función pulmonar, la capacidad de esfuerzo (ergo-metría incremental y prueba de la marcha), la LFE y el volumen telespiratorio (VTE) durante el ejercicio, la función muscular respiratoria, la disnea y la calidad de vida (con el St. George's Respiratory Questionnai-re).

Resultados: Los pacientes (volumen espiratorio forzado en el primer segundo del 31% del valor de referen-cia) tenían moderadamente reducidas la fuerza y la resistencia musculares respiratorias. Diecinueve mos-traban LFE en reposo y 24 al 70% de la carga máxima ($W_{máx}$). El VTE aumentó desde el reposo hasta el 70% de la $W_{máx}$ (un 9% del valor de referencia de la capacidad vital forzada). Al 70% de la $W_{máx}$ el VTE se correla-cionó inversamente con la LFE (rho = –0,42), las resistencias muscular inspiratoria (rho = –0,43) y espira-toria (rho = –0,42) y el consumo máximo de oxígeno (rho = –0,52). El incremento del VTE desde reposo hata el 70% de $W_{máx}$ se correlacionó con la disnea (rho = 0,53), y –la LFE al 70% de $W_{máx}$ con la escala de ac-tividad del St. George's Respiratory Questionnaire (rho = –0,56). Fueron predictores independientes del VTE al 70% de $W_{máx}$ el volumen espiratorio forzado en el primer segundo, la resistencia muscular espirato-ria y la LFE.

Conclusiones: En la EPOC avanzada la reducción de la resistencia de los músculos espiratorios está relacio-nada con mayor HD (y menor LFE) durante el ejercicio, lo que se asocia a mayor disnea y peor calidad de vida.

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Introduction

In patients with chronic obstructive pulmonary disease (COPD), dynamic hyperinflation (DH) contributes to the onset of dyspnea and limits exercise capacity. In recent years, it has been recognized that inspiratory capacity, as a measure of DH, is a clinically significant variable and a prognostic factor in COPD.[1] DH has both positive and negative physiologic repercussions.[2-4] The negative effects include reduced diaphragmatic efficiency, increased elastic work of breathing, and impairment of diastolic cardiac function. DH does, however, also have a positive effect in that the increase in lung volume gives rise to higher maximal expiratory flow, which in turn opens the small airways, improving ventilation distribution and reducing the resistive work of breathing. On balance, however, DH is negative in terms of both exercise tolerance and breathlessness.

In COPD, the chief mechanism in the development of DH is expiratory flow limitation. Patients with COPD have reduced maximal expiratory flows and many of them are flow-limited even during spontaneous breathing at rest.[5,6] Expiratory flow limitation affects both maximal ventilation and exercise capacity[7] and also favors the development of DH by limiting the speed at which the lung empties.[8] It is difficult to differentiate the repercussions of DH from those of flow limitation because the 2 phenomena are related (flow limitation induces DH and the resulting increase in lung volume reduces the flow-limited portion of the flow-volume curve).

During exercise, healthy individuals generally reduce end-expiratory lung volume (EELV) until they achieve maximal oxygen consumption,[9] but patients with COPD exhibit a number of different patterns, including early hyperinflation, late hyperinflation, and no hyperinflation.[10,11] The clinical repercussions of these patterns remain unclear. They have been attributed to possible differences in the limitation imposed by the degree of expiratory flow limitation, but the percentage of flow limitation was not measured in the studies cited.[10,11]

It has been suggested that a reduction in expiratory muscle activity may play a role in the development of DH during exercise in patients with severe COPD.[11] In effect, the fact that DH is found in patients without flow limitation[2,7] and that some flow-limited patients do not develop DH[12] is evidence that mechanisms other than flow limitation must play a role in the development of DH. Some of these mechanisms may be related to inspiratory muscle function, but weakness of the abdominal muscles—the principal expiratory muscles—may also impair lung emptying.[2] In healthy individuals, there is a wide margin between maximal expiratory pressure (P_{Emax}) and the pressure levels reached during exercise.

Extrapolation of this fact to COPD, and the presence in COPD of a low expiratory flow "ceiling" owing to flow limitation, led researchers to consider it unlikely that the expiratory muscles played an important role in the development of DH during exercise in affected patients.[13] However, it was later demonstrated that patients with advanced COPD recruit abdominal expiratory muscles even at rest, and that the strength and principally the resistance of these muscles is often reduced by the same dysfunction that affects other muscle groups in the context of the systemic manifestations of COPD.[14] There is only scant data in the medical literature concerning the role of the expiratory muscles in the ventilatory response to exercise in COPD, much less than can be found on the role of the inspiratory muscles in general and the diaphragm in particular in this context.

Our objective was to investigate the relationship, if any, between expiratory muscle function and DH during exercise and to ascertain
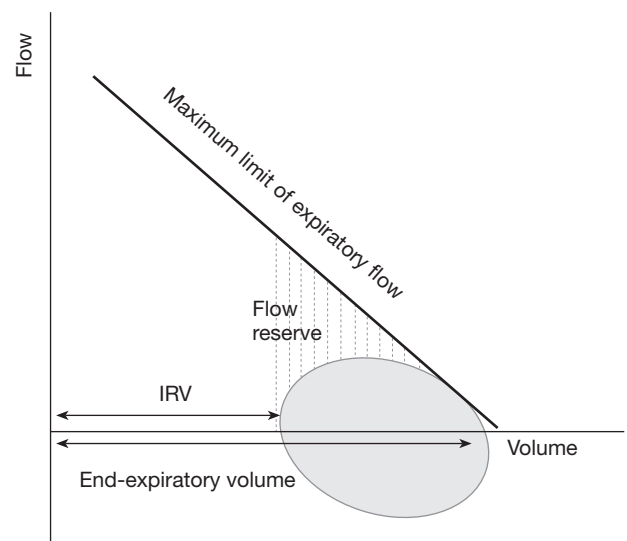

Figure 1. Graphic representation of a flow-volume curve during spontaneous breathing. The expiratory flow rate (positive in the Figure) can be increased by using the flow reserve up to the maximum limit of expiratory flow, after which the corresponding segment of the flow-volume curve will be flow-limited. Alternatively the patient could make use of the inspiratory reserve volume (IRV) and increase end-expiratory lung volume, a strategy that would give rise to dynamic hyperinflation and an increase non–flow-limited expiratory flow. Dynamic hyperinflation is the only option in the presence of maximum expiratory flow limitation (almost 100% of tidal volume).

whether such a relationship would provide any evidence supporting a possible role for muscle dysfunction in the development of DH in patients with advanced COPD, bearing in mind that patients with severe obstruction are very likely to reach flow limitation during exercise and that such limitation would give rise to an increase in EELV, that is, to DH. Our second aim was to study the possible clinical repercussion such a relationship might have on exercise capacity, dyspnea, and health-related quality of life. In other words, we asked ourselves whether patients with severe or very severe COPD use all their expiratory flow reserves (flow limitation) to increase ventilation during exercise or, alternatively, make early use of their inspiratory reserve volume (DH) (Figure 1), and whether expiratory muscle function plays any role in the ventilatory strategy used by these patients, and what the clinical implications of such involvement might be.

Patients and Methods

Patients

We studied clinically stable patients with COPD who had a forced expiratory volume in 1 second (FEV_1) under 50% of predicted. Subjects were selected consecutively from among patients waiting to start a pulmonary rehabilitation program in the participating centers. Most of the patients participated simultaneously in other research projects relating to muscle training in COPD, some of the results of which have already been published.[15,16] The study protocol was approved by the ethics committees of the participating institutions, and all the patients gave their informed consent. Patients who met any of the following criteria were excluded from the study: an increase in FEV_1 greater than 400 mL after administration of 200 μg of inhaled salbutamol; hemoglobin saturation under 90%; a body mass index below 20 kg/m² or greater than 35 kg/m². Also excluded were patients presenting significant comorbidities that might interfere with the results, such as neoplastic, cardiovascular, neuromuscular, osteoarticular, or metabolic disease, alcoholism or severe malnutrition, and patients receiving pharmacological therapy that could affect muscle function (for example, theophylline or systemic corticosteroids). To exclude patients with obstructive sleep apnea-hypopnea syndrome, we evaluated symptoms and performed night-time pulse oximetry. All the parameters listed below were measured within an interval of 2 to 3 days.

Anthropometric Data, Quadriceps Strength, and Lung Function

We measured height, body weight, arm circumference, and tricipital skinfold (in the middle third of the brachial muscle), and assessed the strength of the quadriceps in the nondominant limb by dynamometry. The following were also performed following current guidelines: spirometry and measurement of 12-second maximum voluntary ventilation with a Fleisch-type pneumotachometer (Datospir 92; Sibelmed, Barcelona, Spain); measurement of static volumes by body plethysmography; and carbon monoxide single breath diffusing capacity (Datalab 500; Sensor-Medics, Yorba Linda, California, USA). We used reference values validated for a Mediterranean population.[17,18]

Strength and Endurance of Respiratory Muscles

We measured maximal inspiratory pressure (P_{Imax}) from residual volume and maximal expiratory pressure (P_{Emax}) from total lung capacity using a manometer (model 192; Sibelmed, Barcelona, Spain), and compared the results obtained with reference values established by Morales et al.[19] Respiratory muscle endurance was assessed by measuring the inspiratory and expiratory pressures reached during incremental load testing with threshold valves ($PIth_{max}$ and $PEth_{max}$, respectively) and by measuring how long the patient could tolerate an inspiratory or expiratory load equivalent to 80% of the $PIth_{max}$ or $PEth_{max}$ ($TIth_{80}$ and $TEth_{80}$, respectively). The methods, equipment, and reference values used have already been described in detail.[14,20,21]

Incremental Exercise Testing

An incremental symptom-limited cycle ergometer test was performed (Collins-CPX, Braintree, Massachusetts, USA) with increments of 16 W/min.[22] The following were recorded throughout this test: electrocardiogram, ventilatory variables, breath-by-breath oxygen and carbon dioxide in exhaled air, and hemoglobin oxygen saturation measured by pulse oximetry. In addition, leg discomfort and dyspnea (modified Borg scale) were measured every 2 minutes throughout the test.

Measurement of Expiratory Flow Limitation and EELV During Exercise

Cycle ergometer submaximal tests were carried out at 50% and 70% of the maximum load achieved during the incremental test. With the patient at rest and sitting on the cycle ergometer and after 3 minutes of pedaling at each of the 2 loads, we determined whether or not the patient was flow-limited and quantified the percentage of tidal volume affected ($\% V_T$) by applying negative expiratory pressure and the change in EELV by measuring inspiratory capacity.[5,23] The equipment used has been described in detail in an earlier study.[9] Briefly, the technique consists in comparing, by way of superimposition, the flow-volume curve obtained while applying negative expiratory pressure (3 cmH_2O) with the curve obtained during the preceding respiratory cycle; flow limitation was defined as the coincidence of a segment of the curve for the test breath with that of the control breath (a difference in flow <0.07 L/s was deemed negligible).[24] At least 3 measurements were made at each exercise level studied. At each level the patient was connected to the system by way of a cylindrical mouthpiece and the flow-volume curves were recorded graphically in real time using a computer program specifically designed to execute the task (Datospir 500, Sibelmed, Barcelona, Spain). Negative pressure was applied immediately after the start of expiration once the breathing pattern had become regular and was maintained until expiration was complete. Maneuvers with artifacts were discarded, as were those in which the flow in the negative pressure cycle was lower than that of the control curve (an indication of partial collapse of the upper airway).

Three inspiratory capacity maneuvers were also performed at each exercise level with the same equipment used to measure EELV. EELV was expressed as a percentage of predicted forced vital capacity (FVC) in order to standardize the value (EELV = 1–(predicted FVC–IC) × 100/predicted FVC). Thus, an EELV of 100% would correspond to total lung capacity and any figure higher than that would indicate DH. Inspiratory capacity maneuvers were deemed acceptable as long as intermaneuver variability remained below 150 mL and when sufficient effort was made and the results were free of artifacts. We calculated the average of the technically correct maneuvers for the breathing pattern variables, flow limitation ($\% V_T$), and inspiratory capacity.[3]

Six-Minute Walk Test

The best of 2 walk tests performed in accordance with current guidelines was used. During these tests, hemoglobin oxygen saturation and heart rate were recorded by pulse oximetry. Perceived dyspnea before and after testing were also recorded (modified Borg scale).

Dyspnea and Health-Related Quality of Life

Dyspnea related to activities of daily living was assessed on the modified Medical Research Council (MRC) scale (0, no breathlessness; 4, very intense dyspnea).[25] Quality of life was measured with the Saint George's Respiratory Questionnaire (SGRQ),[26] a tool that scores from 0 to 100 in 4 scales (symptoms, activity, impact, and overall) representing the range from no effect to maximum effect on the patient's quality of life.

Statistical Analysis

Except when otherwise indicated, values are expressed as arithmetic means (SE). The Mann Whitney U test was used for comparisons between the groups, and within-group comparisons were performed with the Wilcoxon signed-rank test or 1-way analysis of variance followed by the Duncan post hoc test. Correlations between variables were analyzed with the Spearman correlation coefficient (ρ). The relationship between respiratory muscle function variables and the clinical variables, expiratory flow limitation, and DH was assessed by calculating partial correlation coefficients; the significant variables were controlled in the simple correlation analysis. Multiple linear regression (stepwise forward) was used to select the independent predictors of EELV during exercise from among the anthropometric, lung function, and respiratory muscle variables. The level of statistical significance was set at a value of *P* less than .05.

Results

Patient Characteristics

The characteristics of the 25 patients enrolled in the study are shown in Table 1. The low mean inspiratory capacity (77% [4%] of predicted) of the group is an indication of a certain level of

hyperinflation even during resting quiet breathing (Table 2). Nineteen patients (76%) were flow-limited at rest (46% [5%] V_T; range, 15%–71%). Patients who were not flow-limited at rest reported greater dyspnea at the maximum exercise level (Figure 2) and scored higher on the SGRQ impact scale in the absence of any other statistically significant differences in anthropometric, clinical, or functional variables.

Dynamic Hyperinflation and Expiratory Flow Limitation During Exercise

Table 2 shows the ventilatory variables before exercise and at the 2 submaximal workloads studied. All of the patients exhibited progressive DH during exercise, and no differences were observed in this respect between those with and without flow limitation at rest (Table 2 and Figure 3). The increase in mean EELV from rest to 70% of peak workload (W_{max}) was 0.388 L (range, −0.15 L-1.03 L). We divided the patients into 2 groups according to whether the increase in EELV during exercise was less than or more than 150 mL (the figure we used as the threshold to define DH in light of the variability of the technique). We observed DH in 20 cases (84%).[3] No significant differences in the variables studied were observed between the group of 20 patients who exhibited DH and the 5 who did not. Of these 5 patients, 3 exhibited a high degree of flow limitation (V_T, >50%) both at baseline and during exercise (FEV_1, 26% and 38% of predicted, respectively) and 1 was only flow-limited at 70% of W_{max} (V_T, 32%; FEV_1, 38% predicted). The remaining patient–the only one not flow–limited at any of the levels studied–had the highest resting EELV of the 20 patients (FVC, 55% predicted; FEV_1, 21% of predicted; carbon monoxide transfer coefficient [carbon monoxide transfer factor/alveolar volume], 15% of predicted); and maximal oxygen consumption, 18% of predicted. As would be expected, the patients with the highest level of DH in proportion to their increase in ventilation during exercise also had a higher EELV, (ΔEELV/Δventilation correlated with EELV at 70% of absolute W_{max}; ρ=−0.59,

Table 1
Patient Characteristics[a]

	Total (n=25)	Not Flow-Limited at Rest (n=6)	Flow-Limited at Rest (n=19)	P
Age, y	64 (1)	61 (2)	66 (2)	NS
BMI, kg/m^{-2}	26.5 (1.2)	25.4 (1.5)	27.2 (1.6)	NS
FVC, % predicted	65 (2)	66 (4)	62 (4)	NS
FEV$_1$, % predicted	31 (2)	30 (3)	31 (2)	NS
TLC, % predicted	121 (3)	122 (4)	121 (4)	NS
RV/TLC, %	60 (2)	60 (3)	61 (2)	NS
KCO, % predicted	72 (6)	67 (15)	73 (6)	NS
P$_{Imax}$, % predicted	64 (4)	55 (7)	67 (5)	NS
PIth$_{max}$, % P$_{Imax}$	43 (4)	39 (6)	46 (5)	NS
TIth$_{80}$, min	8.7 (1)	9.3 (1.4)	8.5 (1.3)	NS
P$_{Emax}$, % predicted	68 (4)	69 (6)	67 (6)	NS
PEth$_{max}$, % P$_{Emax}$	53 (4)	49 (10)	56 (6)	NS
TEth$_{80}$, min	10.5 (1.1)	9.5 (1.9)	10.7 (1.3)	NS
VO$_{2max}$, % predicted	71 (5)	58 (10)	75 (6)	NS
VO$_{2max}$, mL,min^{-1},kg^{-1}	14.9 (0.7)	14.1 (1.4)	15.1 (0.8)	NS
W$_{max}$, % predicted	55 (3)	51 (7)	56 (4)	NS
HR$_{max}$, % predicted	82 (2)	78 (4)	84 (3)	NS
V$_{Emax}$, %MVV	93 (4)	85 (10)	96 (6)	NS
6 min walk distance, m	460 (17)	469 (32)	457 (19)	NS
SGRQ, symptoms	56 (5)	55 (11)	57 (5)	NS
SGRQ, activity	66 (4)	73 (8)	64 (5)	NS
SGRQ, impact	44 (3)	57 (4)	40 (4)	.024
SGRQ, overall score	53 (3)	62 (5)	50 (4)	NS

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; HR$_{max}$, maximum heart rate during the incremental cycle ergometry test; KCO, carbon monoxide transfer coefficient (transfer factor/alveolar volume); NS, no significant intergroup difference (*P*< .05); P$_{Emax}$, maximal expiratory pressure; P$_{Imax}$, maximal inspiratory pressure; PEth$_{max}$, maximal expiratory threshold pressure during incremental load testing; PIth$_{max}$, maximal inspiratory threshold pressure during incremental load testing; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TEth$_{80}$, sustained ventilation time against an expiratory load of 80% of the PEth$_{max}$; TIth$_{80}$, sustained ventilation time against an inspiratory load of 80% of the PIth$_{max}$; TLC, total lung capacity; V$_{Emax}$ (% MVV), maximal minute ventilation during incremental cycle ergometry (expressed as a percentage of maximal voluntary ventilation); VO$_{2max}$, maximal oxygen consumption; W$_{max}$, peak workload.

[a] Values are expressed as means (SE).

Table 2
Ventilatory Variables at Rest and During Exercise[a]

	Patients Without EFL at Rest (n=6)			Patients With EFL at Rest (n=19)		
	Resting	50% W_{max}	70% W_{max}	Resting	50% W_{max}	70% W_{max}
V_E, L/min	15 (2)	25 (2)[b]	30 (3)[b]	17 (1)	30 (2)[b]	35 (2)[b]
V_T, mL	861 (112)	1,081 (93)	1,164 (125)[c]	852 (43)	1,059 (38)[c]	1,146 (44)[b]
V_T (%FVC)	28 (5)	35 (4)	38 (4)[c]	27 (2)	34 (2)	35 (2)[c]
RR, bpm	19 (3)	24 (2)	26 (2)	21 (1)	28 (1)[b]	31 (2)[b]
T_I/T_{TOT},%	43 (2)	38 (2)	39 (1)	39 (1)	37 1	36 1
V_T/T_I (L/s)	0.59 (0.06)	1.38 (0.08)[b]	1.28 (0.12)[b]	0.75 (0.05)	1.09 (0.06)[b]	1.63 (0.09)[b]
V_T/T_E (L/s)	0.44 (0.06)	0.80 (0.06)[b]	0.82 (0.09)[b]	0.47 (0.05)	0.67 (0.05)[b]	0.93 (0.07)[b]
EFL, %V_T	0	14 (8)	22 (8)	46 (5)[d]	49 ± 4[d]	43 (6)
EILV (% predicted FVC)	75 (3)	86 (3)[b]	90 (1)[b]	72 (2)	86 ± 1[b]	87 (2)[b]
EELV (% predicted FVC)	55 (4)	60 (5)	64 (3)[b]	51 (2)	61 (2)[b]	60 (2)[c]

Abbreviations: bpm, beats per minute; EFL, expiratory flow limitation; FVC, forced vital capacity; RR, respiratory rate; T_I/T_{TOT}: ratio of mean inspiratory time to total time of the respiratory cycle; V_E, minute ventilation; V_T/T_E, mean expiratory flow rate; V_T/T_I, mean inspiratory flow rate; V_T: tidal volume; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; W_{max}, peak workload during incremental exercise test.

[a] Values are expressed as means (SE).
[b] $P<.01$ compared to the resting value.
[c] $P<.05$ compared to the resting value.
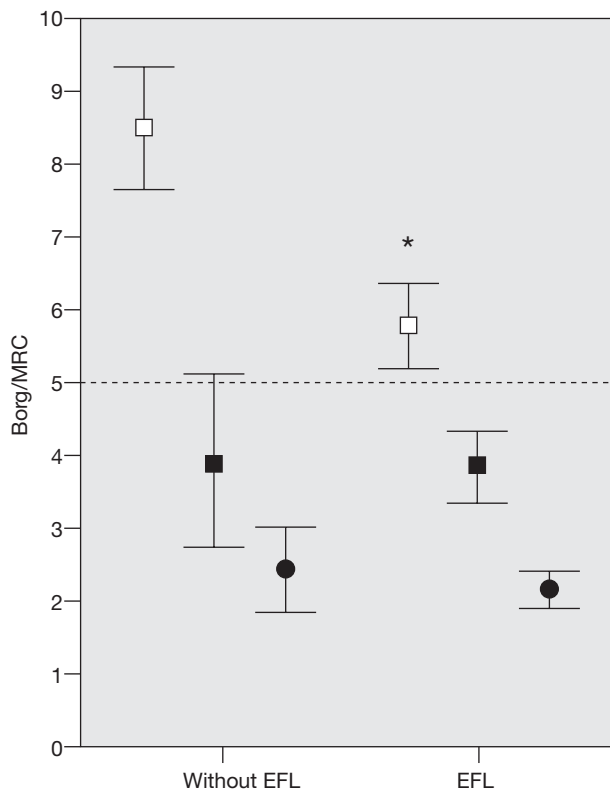[d] $P<.05$ compared to the group without EFL at rest.

Figure 2. Comparison of dyspnea variables between individuals with and without expiratory flow limitation (EFL) at rest. Mean dyspnea score on the Borg scale measured at the end of the incremental cycle ergometry test (empty squares) and at the end of the 6-minute walk test (black squares). Mean dyspnea measured on the modified Medical Research Council (MRC) scale (black circles; the dotted line indicates the maximum score on the MRC scale). The interval lines represent the standard error in each case. *$P<.05$ between groups.
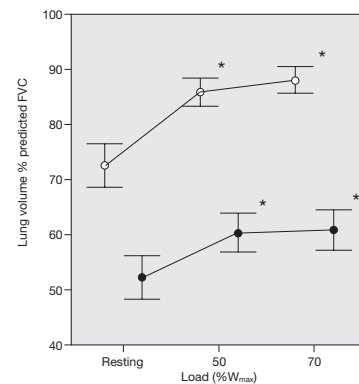

Figure 3. Evolution of lung volumes by exercise workload in the 25 patients. One hundred percent of forced vital capacity (FVC) corresponds to total lung volume. The points represent the group means (empty circles for end-inspiratory volume and black circles for end-expiratory volume) and the interval lines represent the standard error in each case. The distance between end-inspiratory and end-expiratory volumes for each workload represents tidal volume. %W_{max} indicates the percentage of peak workload. *$P<.05$ with respect to the resting value.

flow limitation at rest, 3 had no limitation at 50% of W_{max} and only 1 had no limitation at 70% of W_{max} (see the description of this patient in the preceding paragraph). There was a significant correlation between flow limitation at rest and at 70% of W_{max}, although with considerable dispersion of data (Figure 4A).

Clinical and Physiological Correlations

A higher degree of flow limitation at 70% of W_{max} correlated with increased exercise capacity, less dyspnea, and better respiratory muscle function (Table 4 and Figures 4B and 4C). The ΔEELV during exercise (from resting to 70% of W_{max}) correlated positively with dyspnea assessed using the MRC scale (ρ=0.53, P=.008), and a higher EELV at 70% of W_{max} was associated with greater obstruction and air trapping, reduced exercise capacity, less inspiratory and expiratory muscle endurance and, as mentioned above, greater flow limitation at 70% of W_{max} (Tables 3 and 4).

Multivariate analysis (Table 5) identified FEV_1, $PEth_{max}$ and level of flow limitation at 70% of W_{max} as the independent variables that explained the variability of EELV at 70% of W_{max} (R^2 of the model = 0.74).

P=.04). An inverse correlation was found between EELV at 70% of W_{max} and flow limitation at 70% of W_{max} (Table 3).

Baseline expiratory flow limitation remained stable or increased with exercise (Table 2) in all but 6 patients; the only distinctive characteristic of that subgroup was that they had a significantly lower $PEth_{max}$ than the other patients (56 [8] vs 71 [6] cmH$_2$O; P=.013, and 43% [2%] vs 56% [5%] of PE_{max}; P=.005). Of the patients without

Table 6 shows the significant correlations in expiratory muscle function after adjustment for age, height, weight, FVC, FEV$_1$ carbon monoxide transfer coefficient, P$_{Imax}$, and PIth$_{max}$.

Discussion

The main findings in the present study of patients with severe or very severe COPD were as follows: *a)* expiratory flow limitation and DH occur very frequently but to varying degrees during submaximal exercise and are inversely associated in magnitude; *b)* expiratory muscle endurance is an independent predictor of DH during exercise, and correlates inversely with this variable; and *c)* the presence of flow limitation at rest does not imply more dyspnea, lower exercise capacity, or a poorer health-related quality of life in these patients, and a higher percentage of flow limitation during exercise is associated with less dyspnea, greater exercise tolerance, and better health-related quality of life, an association possibly mediated by the development of less DH.

Most of the patients were flow-limited at rest, as would be expected in view of the severity of the COPD (FEV$_1$ between 19% and 48% of predicted). We believe that the severity of disease in this group explains the greater prevalence of flow limitation compared to other published series.[5,6,27] However, despite the apparent

homogeneity of the sample population with respect to other lung function variables, the high intersubject variability in the percentage of tidal volume affected by flow limitation is evidence that the degree of flow limitation is the result of the interaction of several other factors in addition to the degree of obstruction and flow resistance. These additional factors undoubtedly include ventilatory pattern and distensibility of the chest wall and lungs.[2,6-8,13] Our patients exhibited moderate hyperinflation and air trapping at rest whether or not they were flow-limited. Moreover, inspiratory capacity was comparable in both the patients with and without flow limitation at rest (80% and 76% of predicted, respectively). If increased EELV were an "obligatory" response to the limit imposed by flow limitation, hyperinflation should not be found in patients without flow limitation. Our findings suggest that other mechanisms are involved in the increase in lung volume,[2,8] in the same way that the response to bronchoconstriction in patients with asthma can result in hyperinflation in the absence of flow limitation.[28] We were unable to find any significant functional differences in our patients that would explain why some of them reached maximal expiratory flow (expiratory flow limitation) at rest and others did not (Table 1 and Figure 1). Consistent with the findings reported in the literature, in most cases the hyperventilation produced by exercise was accompanied by an increase in flow limitation, and almost all the

Table 3
Significant Correlations With End-Expiratory Lung Volume During Exercise at 70% of Maximum Work Rate[a]

Variables	ρ
FVC, % predicted	−0.43
FEV$_1$, % predicted	−0.67
RV/TLC, %	0.58
6 min walk distance, m	−0.43
W$_{max}$, % predicted	−0.48
VO$_{2max}$/kg	−0.52
VO$_{2max}$/W$_{max}$	0.42
PIth$_{max}$	−0.43
PEth$_{max}$	−0.42
EFL 70% W$_{max}$, %V$_T$	−0.42

Abbreviations: EFL 70% W$_{max}$ (% V$_T$), expiratory flow limitation as a percentage of tidal volume; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEth$_{max}$, maximum expiratory pressure tolerated during incremental load testing; PIth$_{max}$, maximum inspiratory pressure tolerated during incremental load testing; RV, residual volume; TLC, total lung capacity; VO$_{2max}$, maximal oxygen consumption; W$_{max}$, maximal work rate during incremental exercise testing.

[a] The level of statistical significance was set at a value of *P*<.05. for all the correlations.

Table 4
Significant Correlations With the Percentage of Expiratory Flow Limitation During Exercise at 70% of Maximal Work Rate[a]

Variables	ρ
6 min walk distance, m	0.44
W$_{max}$	0.61
VO$_{2max}$/kg	0.43
VO$_{2max}$/W$_{max}$	−0.42
Dyspnea /W$_{max}$	−0.49
PIth$_{max}$	0.52
PEth$_{max}$	0.46
SGRQ, activity	−0.56

Abbreviations: Dyspnea/W$_{max}$, dyspnea score at the end of the incremental exercise test (Borg) divided by the maximal work rate achieved; PEth$_{max}$, maximal expiratory pressure tolerated during incremental load testing; PIth$_{max}$, maximal inspiratory pressure tolerated during incremental load testing; SGRQ, St George's Respiratory Questionnaire; VO$_{2max}$, maximal oxygen consumption; W$_{max}$, maximal work rate during incremental exercise testing.

[a] The level of statistical significance was set at a value of *P*<.05. for all the correlations.
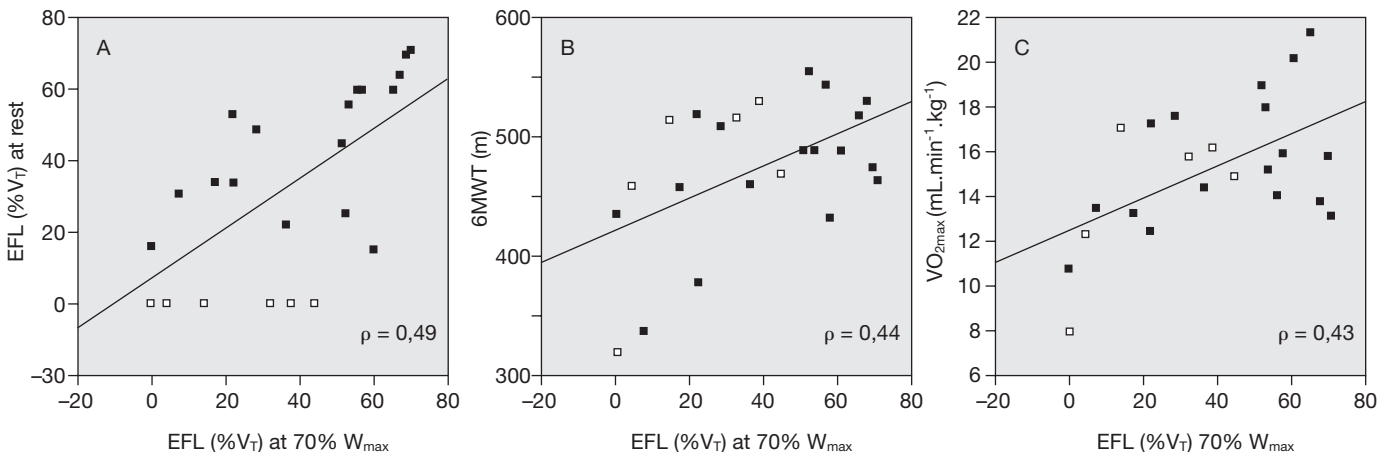

Figure 4. Relationship between expiratory flow limitation (EFL) during exercise at 70% of peak workload (W$_{max}$) and EFL at rest *(A)*, distance walked in 6 minutes (6MWT) *(B)* and maximal oxygen consumption (VO$_{2max}$) *(C)*. The linear regression lines are shown. The empty squares represent the patients without EFL at rest and the black squares represent the patients who were flow-limited at rest. %V$_T$ indicates percentage of tidal volume affected by EFL; ρ, Spearman correlation coefficient (in all cases, *P*<.05).

Table 5
Multiple Linear Regression for End-Expiratory Lung Volume (EELV)[a]

Dependent Variable	EELV Before Exercise		EELV at 50% of W_{max}		EELV at 70% of W_{max}	
	Variable	β	Variable	β	Variable	β
Independent variables selected	Weight	0.555	FEV_1	0.772	FEV_1	0.534
	$TIth_{80}$	0.372	$TIth_{80}$	0.419	$PEth_{max}$	0.448
			$PEth_{max}$	0.317	EFL	0.306
R^2	0.582		0.718		0.741	

Abbreviations: FEV_1, forced expiratory volume in the first second; EFL, expiratory flow limitation; $PEth_{max}$, maximal expiratory pressure tolerated during incremental load testing; $TIth_{80}$, sustained ventilation time against an inspiratory load 80% of the maximum load achieved during incremental testing; W_{max}, maximal work rate during incremental exercise testing.
[a] A positive β value indicates greater distance from total lung capacity (less dynamic hyperinflation).

Table 6
Significant Partial Correlations With Expiratory Muscle Function[a]

Dependent Variables	Independent Variables and Partial Correlation Coefficients			
	Exercise		Dyspnea and Quality of Life	
P_{Emax}	W_{max}	0.62	MRC score	−0.70
$PEth_{max}$	W_{max}	0.64	Symptoms	−0.56
	6MWT	0.59	SGRQ	−0.60
	CDH	−0.78		

Abbreviations: 6MWT, distance walked in the 6-minute walk test; CDH, coefficient of dynamic hyperinflation (increase in end-expiratory lung volume/increase in ventilation during exercise between 50% and 70% of the maximum load during incremental load testing); MRC, Medical Research Council; P_{Emax}, maximal expiratory pressure; $PEth_{max}$, maximal expiratory pressure tolerated during incremental load testing; SGRQ, St George's Respiratory Questionnaire; W_{max}, maximal work rate during incremental exercise testing.
[a] The level of statistical significance was set at a value of $P<.05$ for all the correlations.

patients were flow-limited at the highest exercise level studied.[7,13,29] The merely moderate correlation found between flow limitation at rest and at 70% of W_{max} can be explained by normal exercise-induced changes, such as hyperventilation and changes associated with lung volumes obviously, but also changes in posture relating to the neck and chest wall, changes in airway caliber and lung distensibility (for example, alterations in lung perfusion), and possibly the onset of exercise-related respiratory muscle fatigue.[13,31] Overall, the patients displaced their EELV towards total lung capacity during exercise, but greater DH was associated with a lower percentage of flow limitation. In other words, the patients who made less use of their expiratory flow reserves (who displayed less flow limitation) made more use of their lung volume reserves (developed greater DH, Figure 1). The mechanisms that favor the development of DH act in 2 ways: *a)* by hindering expiration (increased airway resistance, persistent contraction of the inspiratory muscles during expiration, and chronic adaptation of the diaphragmatic muscle fibers to short-duration work); or *b)* by shortening expiratory time (it has been proposed that a reflex mechanism terminates expiration once the maximal expiratory flow rate [flow limitation] has been reached).[2,30] Our results point to the intervention of the expiratory muscles as a factor reducing DH in severe to very severe COPD (see below).

Perhaps the most interesting and novel finding of the present study was the relationship observed between greater DH during exercise and lower expiratory muscle endurance. Although it is known that in patients with COPD the abdominal muscles play an important and ever-increasing role during exercise (a large part of the inspiratory function of the diaphragm falls on the accessory muscles and the abdominal muscles are progressively recruited during expiration and often even at rest), expiratory muscle dysfunction in this context has only recently been described and its implications have not yet been studied.[15,31] Our study indicates that, when patients become flow-limited or are just reaching this situation, a greater degree of flow limitation will reduce DH, and that the low resistance (endurance) of the expiratory muscles may be involved in the development of greater DH. This hypothesis is supported by 2 findings, *a)* that $PEth_{max}$ correlated inversely with EELV and directly

with expiratory flow limitation, and was an independent predictor of a greater EELV during exercise (as well as of lower FEV_1 and less flow limitation), and *b)* that the 6 patients in whom flow limitation did not increase during exercise had a lower $PEth_{max}$. The expiratory muscles are susceptible to fatigue during exercise, a phenomenon not yet investigated in patients with COPD, but which has been demonstrated in healthy athletes.[31] The role played by these muscles in reducing EELV will be compromised by fatigue when increased airway resistance must be opposed by the postinspiratory tonic activity of the diaphragm. Although flow limitation limits the increase of expiratory flow, dysfunction of the abdominal respiratory muscles could limit the expiratory flow before it reaches its maximum level during exercise and thus worsen the mechanical situation of the inspiratory muscles.[13,31] The following factors all support this hypothesis: *a)* despite the fact that the expiratory muscles in patients with COPD are recruited even at rest and are, in theory, trained, they often exhibit reduced strength and endurance,[14] as we observed in our patients; *b)* electromyographic signs of fatigue have been detected in patients with COPD dealing with expiratory loads of under 50% of P_{Emax}[14]; *c)* during exercise, the active muscle groups (peripheral and respiratory) compete for blood flow and oxygen,[13,32] and in light of the lower peak oxygen uptake and the high metabolic costs of respiratory work typically observed in these patients,[14] this competition could compromise the supply of oxygen to the muscles; *d)* prolonged fatigue of the abdominal muscles occurs in healthy individuals who sustain ventilation between 55% and 80% of maximum voluntary ventilation for only 2 minutes,[13,33] and all our patients exceeded the lower limit of this margin and 13 of them the upper limit while pedaling at 70% of their W_{max}; and *e)* after a pulmonary rehabilitation program involving high-intensity exercise training, patients with severe COPD reduced their EELV during exercise by reducing the abdominal compartment, a result that could be explained by the increased intervention of the expiratory muscles.[34]

Alternatively, the association between less DH (and greater expiratory flow limitation) and better expiratory muscle function could be due to the training induced by the work involved in opposing

greater expiratory flow limitation in patients with a higher tolerance to such limitation. This would be an indication that the expiratory muscles are susceptible to functional improvement when appropriately exercised. This was demonstrated by Weiner et al,[35] who applied a program of expiratory muscle training designed specifically for patients with COPD and found that functional improvement in expiratory muscles was associated with an increase in the distance walked in 6 minutes. The authors of another study also reported an improvement in this variable and in addition decreased dyspnea, an improvement in health-related quality of life, and a reduction in the ratio of FEV_1 to FVC.[16] The results of the present study, together with those obtained following specific expiratory muscle training, indicate that an improvement in expiratory muscle function could benefit patients with advanced COPD who have flow reserves in part of the tidal volume (a low percentage or no flow limitation), at least in part through a reduction of DH. The correlation between stronger inspiratory muscles and a lower EELV could be the result of the lengthening of these muscles as they work with a smaller lung volume, or may be a confounding factor related to the correlation between inspiratory and expiratory muscle function.[2,34]

In severe or very severe COPD, it appears to be more advantageous to "tolerate" a high percentage of flow limitation than to increase operating lung volume during exercise (Tables 3 and 4, and Figure 4). We question whether flow limitation has the negative effects widely reported in the medical literature; excessive expiratory pressure may reduce venous return, thereby increasing pulmonary vascular resistance and decreasing cardiac output.[13,31] However, when these negative effects are compared to those associated with excessive DH (principally the overload of the inspiratory muscles) the latter would appear to have greater weight. In our patients, we found no correlation between the percentage of flow limitation at rest and the clinical variables studied. By contrast, Eltayara et al[6] found an association between flow limitation at rest and dyspnea, but in a group of patients with a wide range of obstruction, including some patients with an FEV_1 of 80% of predicted (see Figure 3 of Eltayara et al[6]). We agree with Eltayara et al that the clinical impact of flow limitation is basically mediated by DH[3,4,7,36] and that flow limitation is a marker of DH in populations, such as the sample in their study, characterized by a wide range of obstruction. However, in our opinion this is not the case in our selected sample of patients with intense obstruction, most of whom had flow limitation and a similar degree of hyperinflation at rest. The patient's perception of breathlessness influences exercise tolerance and health-related quality of life and correlates directly with the degree of DH in patients with COPD.[27,37] Consistent with this, we observed in our patients that greater EELV during exercise was associated with a higher score on the MRC dyspnea scale, while greater flow limitation during exercise was associated with better exercise tolerance and a lower impact on health-related quality of life (a lower score on the SGRQ activity scale).

One of the limitations of the present study was that the number of patients studied was probably insufficient to show differences between those with and without flow limitation at rest (the latter group was particularly small). The trends observed in the between-group comparison (significant in the case of the SGRQ impact scale) would, if confirmed by the results of a larger study, support the hypothesis that greater flow limitation at rest in patients with advanced-stage COPD is associated with a better clinical picture (less dyspnea, greater exercise tolerance, and better quality of life) and better preserved respiratory muscle function. Moreover, it could be conjectured, in light of our results, that better muscle function could play a causal role, with more functional expiratory muscles giving rise to less DH.

Changes in airway caliber during exercise may give rise to bronchodilation or bronchoconstriction and modify the ceiling for maximal flows. We did not repeat spirometry after exercise to assess such changes, but the technique used to measure flow limitation (the application of negative expiratory pressure) is not affected by such changes[23] because it is based on the comparison of a flow-volume curve obtained while applying negative expiratory pressure with the curve obtained during the preceding respiratory cycle. The physiological scenario is essentially identical in both cycles even during physical activity, with the exception of the external pressure gradient that we add to the inspiration generated by the subjects.[5-7] The negative expiratory pressure technique, which has been validated by measuring transpulmonary pressure,[5] requires no forced maneuvers on the part of the patient, eliminates errors caused by thoracic gas compression, and differences in the previous time and volume history of the breathing cycles, and can be used with the patient in different positions and during exercise.[5,7,23] Given that this technique can give rise to false positives caused by the collapse of a highly compliant upper airway,[38] we took a number of precautions to prevent this problem: *a)* we excluded patients with symptoms or oximetry results suggestive of sleep apnea-hypopnea; *b)* we applied only 3 cmH_2O of negative expiratory pressure (just enough to detect flow increases in non–flow-limited subjects with a minimum increase in upper airway resistance as per the findings of Tantucci et al[39] and corroborating evidence from studies of both healthy subjects and patients carried out in our own laboratory demonstrating that only 2 cm of negative pressure produced detectable and measurable increases in expiratory flow in healthy individuals and patients without flow limitation at rest; unpublished data); and *c)* an experienced observer visually monitored the maneuvers and discarded those with artifacts. Other limitations of the technique, already described in the literature, are a) the breath-to-breath variability of the value obtained,[40] a problem addressed by averaging the results of a series of maneuvers (at least 3) to obtain the result most representative of the real situation, and b) the impossibility of detecting flow limitation in the initial phase of expiration so that the maximum value obtained is approximately 70%V_T, but we do not believe that this fact affects the validity of our results.

From a technical standpoint, performance of repeated inspiratory capacity maneuvers is a valid method of measuring DH during exercise, although one possible source of error is that this method is dependent on patient effort. We implemented a number of precautions (described in the methods section) to prevent such errors.

In conclusion, in patients with severe or very severe COPD, expiratory flow limitation at rest is a common finding and such limitation increases during exercise and correlates inversely with DH. The degrees of flow limitation and DH observed during exercise are highly variable, an indication that these patients resort to a variety of different strategies involving the combined use of expiratory flow reserves and lung reserves to increase ventilation. The strategy of reducing DH and increasing expiratory flow limitation appears to be clinically more advantageous because it is associated with less dyspnea, improved exercise capacity, and a better health-related quality of life. This strategy is associated with greater expiratory muscle endurance, a finding that leads us to postulate that expiratory muscle dysfunction may play a role in the development of DH, a hypothesis that should be further investigated. If this hypothesis were correct, interventions aimed at improving the function of respiratory abdominal muscles, such as the incorporation of specific expiratory training into pulmonary rehabilitation programs, could improve both symptoms and health-related quality of life, particularly in non–flow-limited patients with severe obstruction.

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