

# The Cumulative Effect of Long-Acting Bronchodilators, Exercise, and Inspiratory Muscle Training on the Perception of Dyspnea in Patients With Advanced COPD\*

Paltiel Weiner, MD; Rasmi Magadle, MD; Noa Berar-Yanay, MD; Avi Davidovich, MD; and Margalit Weiner, PhD

**Background:** Dyspnea is a common complaint during daily activities in patients with advanced COPD. The mechanisms underlying dyspnea and the appropriate treatment strategies to relieve it are still not totally understood. We hypothesized that the perception of dyspnea (POD) may be modified by the accumulative effect of bronchodilator therapy, exercise, and inspiratory muscle training (IMT).

**Methods:** Spirometry, submaximal exercise performance, inspiratory muscle strength and endurance, and the POD were assessed before and following three consecutive 6-week periods of therapy with a long-acting bronchodilator (LABD), the LABD plus exercise, and the LABD plus exercise plus IMT in 30 patients with moderate-to-severe COPD.

**Results:** There was a small, statistically insignificant, increase in FEV<sub>1</sub> in the study group (mean [ $\pm$  SEM] increase, 1.42  $\pm$  0.3 to 1.49  $\pm$  0.4 L) following the LABD therapy period, and no additional increase following the two other periods of therapy. There was a significant increase ( $p < 0.05$ ) in the 6-min walk distance following the therapy period with the LABD plus exercise (mean increase, 252  $\pm$  41 to 294  $\pm$  47 m) and an additional small increase following the therapy period with the LABD plus exercise plus IMT period (mean increase, 252  $\pm$  41 to 302  $\pm$  49 m). The decrease in the POD was small and statistically not significant following the therapy periods with the LABD and the LABD plus exercise. The major and statistically significant decrease in the POD was noted following the therapy period with the LABD plus exercise plus IMT.

**Conclusions:** In patients with moderate-to-severe COPD, following sequential periods of therapy with the LABD, the LABD plus exercise, and the LABD plus exercise plus IMT, there is a cumulative benefit in the POD. The most significant improvement was associated with IMT and not with the LABD and exercise training. The FEV<sub>1</sub> was moderately increased following the therapy period with the LABD, and the addition of exercise has most affected the 6-min walk distance. (CHEST 2000; 118:672-678)

**Key words:** COPD; inspiratory muscle training; perception of dyspnea

**Abbreviations:** IMT = inspiratory muscle training; LABD = long-acting bronchodilator; P<sub>imax</sub> = maximal inspiratory pressure; P<sub>mPeak</sub> = peak mouth pressure; POD = perception of dyspnea

In patients with advanced COPD, dyspnea is reported as a limiting factor during exercise testing and as a common complaint during daily activities.<sup>1-3</sup> Dyspnea was recently defined<sup>4</sup> by the medical section of the American Lung Association as "a subjective experience of breathing discomfort that derives

from interactions among multiple physiologic, psychological, social, and environmental factors."

The sensation of dyspnea seems to originate with the activation of sensory systems involved with respiration. However, sensory information is, in turn, relayed to higher brain centers where central processing and contextual, cognitive, and behavioral influences shape the ultimate expression of the evoked sensation. Studies performed in the past have suggested that dyspnea results from a mismatch between central respiratory motor activity and afferent feedback from peripheral sensory receptors in

\*From the Department of Medicine A, Hillel-Yaffe Medical Center, Hadera, Israel.

Manuscript received December 7, 1999; revision accepted March 14, 2000.

Correspondence to: Paltiel Weiner, MD, Department of Medicine A, Hillel-Yaffe Medical Center, Hadera, Israel 38100

the lung, airways, and chest wall structures.<sup>5,6</sup> Dyspnea increases when there is a heightened ventilatory demand<sup>7</sup> or a weakness of the respiratory muscles (mismatch between central respiratory motor output and the achieved ventilation),<sup>8,9</sup> when abnormal ventilatory impedance exists,<sup>10</sup> when an abnormal breathing pattern occurs,<sup>11</sup> and also when hypoxemia<sup>12</sup> or hypercapnia<sup>13</sup> is presented. Recently, it was hypothesized<sup>4</sup> that interventions such as bronchodilator therapy (by reducing ventilatory impedance) and oxygen and exercise therapy (by reducing ventilatory demand) have a cumulative benefit in improving the perception of dyspnea (POD) in patients with chronic lung diseases. In addition, studies investigating dyspnea suggest that the degree of breathlessness subjectively reported by the patients is related to the activity and the strength of the inspiratory muscles.<sup>14,15</sup>

We hypothesized that in patients with COPD, the POD may be modified by the accumulative effect of bronchodilator therapy, exercise, and inspiratory muscle training (IMT), and that the improved POD will result in an improvement in submaximal exercise.

## MATERIALS AND METHODS

### Subjects

Thirty patients, 27 men and 3 women, with spirometric evidence of chronic air flow limitation, and a diagnosis of moderate-to-severe COPD according to the criteria of the American Thoracic Society,<sup>16</sup> were recruited for the study. They all were observed during a 4-week run-in period, while their regular treatment was maintained, to verify stability in their clinical and functional status. Their characteristics are summarized in Table 1.

### Study Design

The study design is shown graphically in Figure 1. During the first 6 weeks, 24 patients were randomized to the study group and

received treatment with a long-acting bronchodilator (LABD) (salmeterol xinafoate, 50 µg bid, via Diskus [Glaxo Wellcome; Research Triangle Park, NC]), while 6 patients (a control group) were randomized to receive a placebo (via the same Diskus but with no active drug). One patient dropped out of the study at this stage because of lack of compliance. In the following 6 weeks of the study, the 23 patients were randomized again to receive treatment either with the LABD and general exercise (18 patients) or the LABD plus sham general exercise training (5 patients). Two patients, one from the study group (no compliance) and one from the control group (disappeared from the follow-up), dropped out of the study at this stage. In the last 6 weeks of the study, the 17 patients in the study group were randomized again to receive treatment either with the LABD, general exercise, and IMT (12 patients) or the LABD, general exercise training, plus sham IMT (5 patients). Again, two patients dropped out of the study at this stage, one from the study group (no compliance) and one from the control group (because of disease exacerbation).

### Tests

All tests were performed before and after each stage of the study.

**Spirometry:** The FVC and the FEV<sub>1</sub> were measured three times on a computerized spirometer (Compact; Vitalograph; Buckingham, UK), and the best trial is reported.

**Submaximal Exercise Test:** The distance the patient was able to walk in 6 min was determined in a measured corridor as described by McGavin and coworkers.<sup>17</sup>

**Respiratory Muscle Strength:** Respiratory muscle strength was assessed by measuring the maximal inspiratory pressure (P<sub>imax</sub>) and maximal expiratory pressure, at residual volume and total lung capacity, respectively, as previously described by Black and Hyatt.<sup>18</sup> The value obtained from the best of at least three efforts was used.

**Respiratory Muscle Endurance:** To determine inspiratory muscle endurance, a device similar to that proposed by Nickerson and Keens<sup>19</sup> was used. Subjects inspired through a two-way valve (Hans-Rudolph; Kansas City, MO), the inspiratory port of which was connected to a chamber and plunger to which weights could be added externally. Inspiratory elastic work then was increased by the progressive addition of 25- to 100-g weights at 2-min intervals, as was previously described by Martyn and coworkers,<sup>20</sup> until the subjects were exhausted and could no longer inspire. The pressure achieved with the heaviest load (tolerated for at least 60 s) was defined as the peak mouth pressure (P<sub>mPeak</sub>).

**Table 1—Characteristics of Patients With COPD\***

Characteristics	Before LABD Therapy		Before LABD + Exercise Training Therapy		Before LABD + Exercise Training + IMT Therapy	
	Study (n = 23)	Control (n = 6)	Study (n = 17)	Control (n = 4)	Study (n = 11)	Control (n = 4)
Age, yr	62.3 ± 2.7	61.7 ± 2.5	63.2 ± 2.3	60.1 ± 2.8	62.5 ± 2.4	61.0 ± 2.7
Weight, kg	70.6 ± 2.2	68.3 ± 2.4	69.7 ± 2.3	70.1 ± 2.2	70.0 ± 2.4	71.2 ± 2.1
Height, m	1.70 ± 3.2	1.68 ± 3.3	1.71 ± 3.5	1.68 ± 3.4	1.69 ± 3.1	1.72 ± 2.9
FVC, L	2.12 ± 0.4	2.06 ± 0.4	2.30 ± 0.5	2.34 ± 0.3	2.35 ± 0.5	2.32 ± 0.4
% predicted	59 ± 3.2	57 ± 3.1	64 ± 3.2	65 ± 3.0	65 ± 2.9	64 ± 3.1
FEV <sub>1</sub> , L	1.42 ± 0.3	1.40 ± 0.2	1.49 ± 0.4	1.47 ± 0.4	1.48 ± 0.4	1.50 ± 0.2
% predicted	33 ± 2.0	32 ± 2.0	35 ± 2.2	36 ± 1.9	35 ± 2.0	35 ± 2.1
6-min walk test distance, m	240 ± 38	244 ± 36	252 ± 41	257 ± 40	294 ± 47	288 ± 44
P <sub>imax</sub> , cm H <sub>2</sub> O	57 ± 3.1	55 ± 2.9	56 ± 2.9	54 ± 2.8	57 ± 3.1	56 ± 2.9

\*Values are expressed as mean ± SEM.

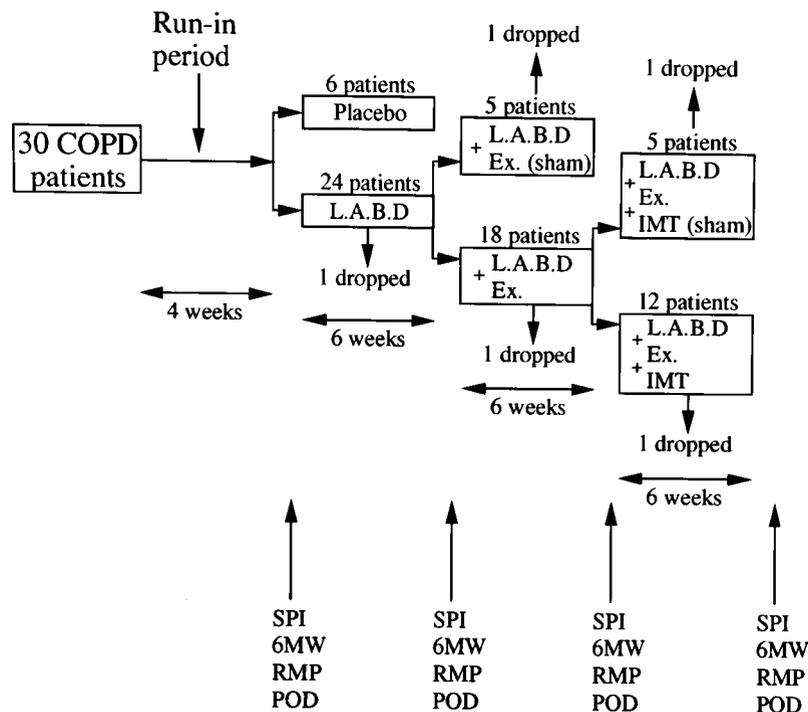


FIGURE 1. The study design. During the first 6 weeks, 24 patients were randomized to receive the LABD, while 6 patients served as a control group. In the following 6 weeks, 23 patients were randomized again to receive treatment either with LABD plus general exercise (18 patients) or the LABD plus sham exercise training (5 patients). In the last 6 weeks of the study, the 17 patients in the study group were randomized again to receive treatment either with the LABD plus general exercise plus IMT (12 patients) or the LABD plus general exercise training plus sham IMT (5 patients). Ex = exercise training; SPI = spirometry; 6MW = 6-min walk test; RMP = respiratory muscle performance test (strength plus endurance).

**POD:** The sensation of dyspnea was measured using the Nickerson and Keens<sup>19</sup> device. The subjects breathed against progressive resistance, at 1-min intervals, in order to achieve a mouth pressure of 0 (no resistance), 5, 10, 20, and 30 cm H<sub>2</sub>O. After breathing for 1 min in each inspiratory load, in a protocol similar to the one previously described by Kikuchi and coworkers,<sup>21</sup> the subjects rated the sensation of difficulty in breathing (dyspnea) using a modified Borg scale.<sup>22</sup> This is a linear scale of numbers ranking the magnitude of difficulty in breathing, ranging from 0 (none) to 10 (maximal).

#### Training Protocol

Subjects trained three times a week, and each session consisted of 1 h of training, performed under the supervision of a physiotherapist.

#### Exercise Training

Both groups received exercise training that consisted of the following: (1) 30 min of cycling on cycle ergometer (subjects started cycling with low load that was then gradually increased, about 5% each session, through the first month, to 50% of the maximal work achieved on the initial progressive exercise test; cycling was then continued at this load); (2) 15 min of rowing on a rowing machine with a low resistance; and (3) 15 min of exercises aimed to strengthen the upper and lower extremities and abdominal muscles. When only exercise training was per-

formed, the patients trained the whole hour, and when IMT was added, exercise training was cut to 30 min.

#### IMT

The subjects received either IMT or sham training for 30 min, with a threshold inspiratory muscle trainer (HealthScan Threshold Inspiratory Muscle Trainer; Tri-anim Health Services; Sylmar, CA). Subjects started breathing at a resistance equal to 15% of their P<sub>imax</sub>, for 1 week. The resistance then was increased incrementally, 5% each session, to reach 60% of their P<sub>imax</sub> at the end of the first month. IMT then was continued at this level of resistance. Patients who received sham training breathed through the same inspiratory muscle trainer with no resistance.

## RESULTS

### Spirometry

The mean baseline FEV<sub>1</sub> was almost identical for the study and the control group (Table 1). Following 6 weeks of salmeterol xinafoate treatment, there was a small, but statistically insignificant, increase in FEV<sub>1</sub> in the study group (mean [± SEM] increase, 1.42 ± 0.3 to 1.49 ± 0.4 L) but not in the control group. Following the therapy periods with the

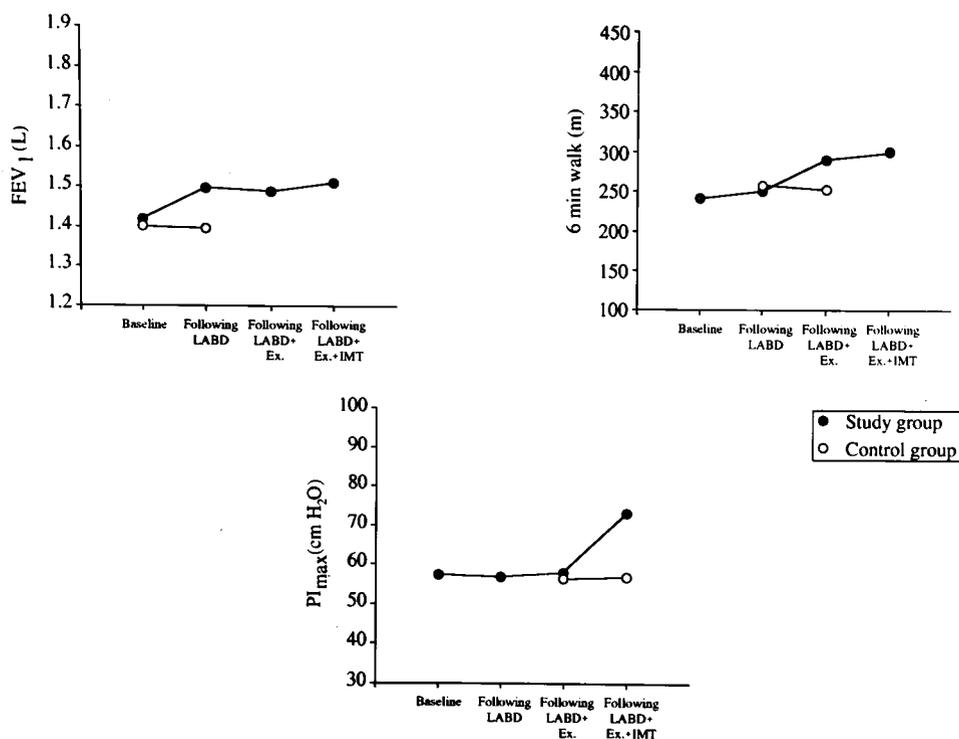


FIGURE 2. The mean levels at baseline and following the three treatment periods of the FEV<sub>1</sub>, the distance walked in 6 min, and the P<sub>imax</sub>. See Figure 1 legend for abbreviation.

LABD plus general exercise and the LABD plus general exercise plus IMT, there was no additional change in the FEV<sub>1</sub> level, either in the study group or in the control group (Fig 2).

#### 6-Min Walk Test

There was no difference between the two groups in the 6-min walk test before the study (Table 1). There was no increase in the distance walked following LABD therapy in either group. However, there was a significant increase ( $p < 0.05$ ) in the distance walked following the therapy period with the LABD plus exercise (mean increase,  $252 \pm 41$  to  $294 \pm 47$  m) and an additional small increase after the therapy period with the LABD plus exercise plus IMT ( $252 \pm 41$  to  $302 \pm 49$  m; Fig 2).

#### Respiratory Muscle Strength and Respiratory Muscle Endurance

Therapy with the LABD and the LABD plus exercise did not change the respiratory muscle strength and endurance. Before the therapy period with the LABD plus exercise plus IMT, there was no difference in the P<sub>imax</sub> or in the P<sub>mPeak</sub>/P<sub>imax</sub> ratio between the study and control groups. Following the therapy period with the LABD plus exercise

plus IMT, there was a statistically significant increase ( $p < 0.005$ ) in the P<sub>imax</sub> and the P<sub>mPeak</sub>/P<sub>imax</sub> ratio in all subjects of the study group but not in the control group. The inspiratory muscle strength, as assessed by the P<sub>imax</sub>, increased from  $57 \pm 3.1$  to  $71 \pm 3.9$  cm H<sub>2</sub>O, and the inspiratory muscle endurance, as assessed by the P<sub>mPeak</sub>/P<sub>imax</sub> ratio, increased from  $57 \pm 4.1\%$  to  $77 \pm 4.5\%$  (Fig 3).

#### POD

The POD, as assessed by the mean Borg score during breathing against resistance, was modified by the accumulative effect of bronchodilator therapy, exercise, and specific IMT. However, the decrease in the POD was small and statistically not significant following the therapy periods with the LABD and the LABD plus exercise. The major and statistically significant decrease in the POD was noted following the therapy period with the LABD plus exercise plus IMT (Fig 4).

#### DISCUSSION

Our study shows that following sequential periods of therapy with the LABD alone, the LABD plus exercise, and the LABD plus exercise plus IMT,

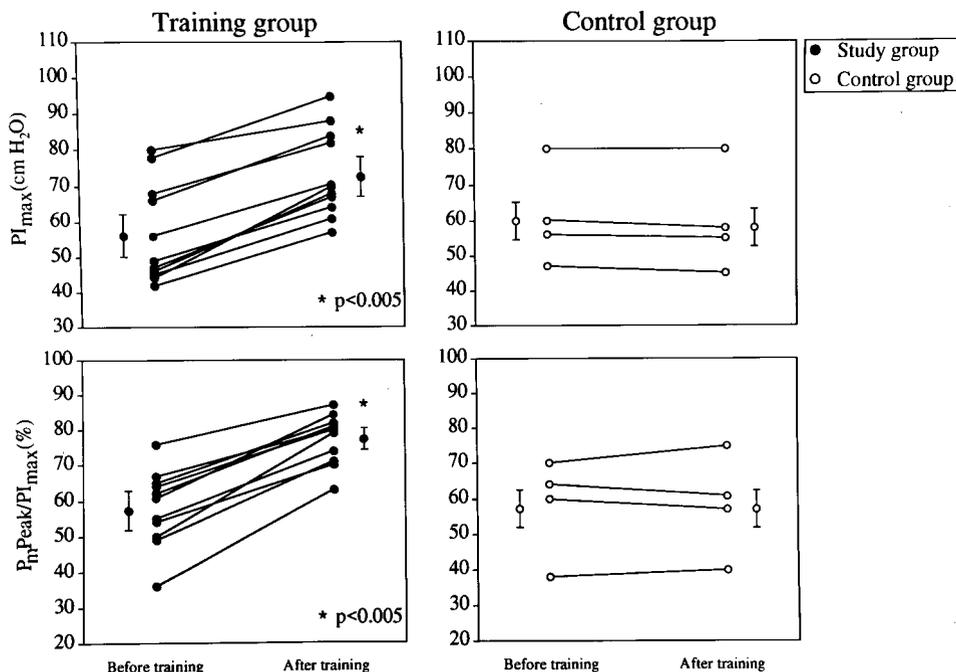


FIGURE 3. Inspiratory muscle strength, as expressed by the  $P_{I\max}$  at residual volume, and inspiratory muscle endurance as expressed by the relationship between the  $P_{mPeak}$  and the  $P_{I\max}$ , before and following 6 weeks of IMT in the control group and in the training group.

there is a cumulative benefit in the POD in patients with COPD. However, the most significant improvement was associated with IMT, and not with the LABD and exercise training. The  $FEV_1$  level was moderately increased (5%) following the LABD therapy period. No further increase was noted during the therapy periods with the LABD plus exercise and the LABD plus exercise plus IMT. The addition of exercise most affected the 6-min walk distance,

while the inspiratory muscle strength mainly increased during the period when IMT was added.

The physiologic basis for the treatment of dyspnea is rooted in the mechanisms underlying shortness of breath. Bronchodilators that reduce mechanical loading (which improves ventilatory capacity) and exercise training that reduces ventilatory demand (relative to capacity) and strengthens weakened inspiratory muscles should relieve dyspnea in patients with COPD.<sup>4</sup>

Inhaled  $\beta_2$ -adrenergic agonists already have been shown to improve dyspnea in patients with COPD.<sup>23</sup> However, the clinical difference of their symptom scores was difficult to interpret. In a more recent study, Ramirez-Venegas and coworkers<sup>24</sup> have also shown that salmeterol reduces dyspnea in patients with COPD. However, this improvement was small, was measured only in patients in the acute state, and was associated with a marked improvement in the  $FEV_1$  (> 20%). In our study, which measured those parameters following long-term administration of the LABD, the improvement in the  $FEV_1$  was only about 5%, and no significant improvement in the POD was detected. Nevertheless, the improvement in  $FEV_1$  was greater during the LABD therapy period than in the following periods.

Many patients with pulmonary disease have an accelerated ventilatory response to exercise that

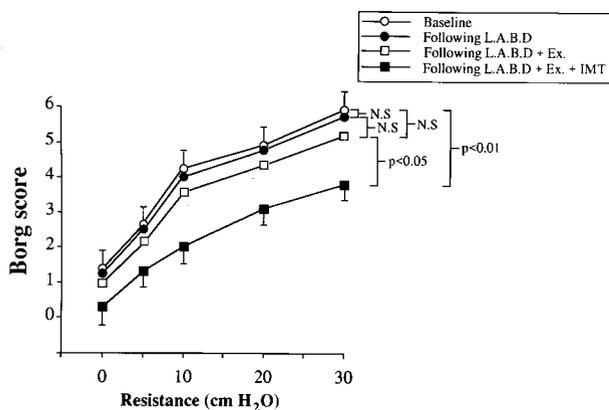


FIGURE 4. Mean  $\pm$  SEM POD (Borg score) during breathing against resistance in the study group, before and following the three treatment periods. NS = not significant; see Figure 1 legend for abbreviation.

causes them to prematurely reach their low maximal ventilatory capacity.<sup>25</sup> Therefore, it can be assumed that exercise training that reduces minute ventilation may translate into improved exertional dyspnea. It has been shown that exertional dyspnea decreases in response to exercise training.<sup>26,27</sup> However, these studies have shown improved exertional dyspnea during maximal exercise, which may not be translated to decreased dyspnea during rest or daily activity. In our study, exercise training was the major factor in improving submaximal exercise (as was assessed by the 6-min walk test) and had only marginal effect on the POD, although the duration of exercise training in our study was only 6 weeks and the POD might have been affected more by a longer training period.

Studies investigating dyspnea suggest that dyspnea, at least in part, is perceived as respiratory muscle effort.<sup>8,9</sup> In addition, a number of studies have been carried out in order to correlate dyspnea and respiratory muscle performance. It is well documented that the degree of breathlessness subjectively reported by the patients is related to the activity and the strength of the inspiratory muscles,<sup>14,15</sup> and that the respiratory muscles can be successfully trained.<sup>28-30</sup> There is some evidence that IMT leads to a decrease in the intensity of dyspnea. Harver and colleagues<sup>31</sup> and Kim and colleagues<sup>32</sup> showed a consistent improvement in dyspnea indexes and fewer symptoms of dyspnea in patients with COPD following IMT. However, in a recent study performed by Marin and colleagues,<sup>27</sup> it was suggested that the motoneural output of the respiratory system in an individual is the most important contributory factor to the sense of dyspnea during exercise in patients with severe COPD. No relationship between respiratory muscle dysfunction and the perception of exertional dyspnea was demonstrated. Therefore, Marin et al<sup>27</sup> concluded that those patients with dyspnea may be candidates for central output modulation rather than, for example, for increasing the respiratory muscle efficiency. Again, exertional dyspnea during maximal exercise was assessed in the study. In our study, IMT was the most significant factor in improving the POD while the submaximal exercise capacity (as assessed by the 6-min walk test) and the FEV<sub>1</sub> were much less affected.

Patients with COPD are frequently limited in their activities by dyspnea, with reduction in functional status and quality of life. A comprehensive rehabilitation program, along with a strategic pharmacologic approach, can now improve both the quality and length of life in patients with symptomatic COPD. Our study showed that while the FEV<sub>1</sub> is most affected by the LABD, the submaximal

exercise capacity is most affected by exercise training, and the POD is most affected by IMT.

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