Clinical Investigations

Respiration

Respiration 2006;73:151–156
DOI: 10.1159/000088095

Received: November 10, 2004
Accepted after revision: March 14, 2005
Published online: September 6, 2005

Inspiratory Muscle Training May Increase Peak Inspiratory Flow in Chronic Obstructive Pulmonary Disease

Paltiel Weiner Margalit Weiner

Department of Medicine A, Hillel Yaffe Medical Center, Hadera, Israel

For editorial comment see p. 143

Key Words

Chronic obstructive pulmonary disease · Dry powder inhalers · Inspiratory muscle strength · Inspiratory muscle training · Peak inspiratory flow

Abstract

Background: When choosing a specific inhalation device for a chronic obstructive pulmonary disease (COPD) patient, the internal airflow resistance and the ability of the patient to overcome it and to create an optimal inspiratory flow are essential. The purpose of the present study was to investigate: (1) the peak inspiratory flow (PIF) that a patient with COPD can generate while breathing through two dry powder inhalers and (2) whether in patients with low PIF specific inspiratory muscle training (SIMT) will increase the PIF and exceed the minimal PIF that is considered necessary to guarantee optimal lung deposition of the drug. ***Methods:*** Inspiratory muscle strength and PIFs were measured in 60 patients with COPD. Then 28 patients with severe COPD and low PIF were randomized to receive SIMT or to a control group. ***Results:*** With the Turbuhaler, 12 patients (20%) could not generate the optimal flow of 60 l/min. PIF correlated very well with maximal inspiratory mouth pressure (PI_{max}) for the Diskus and the Turbuhaler, as well as for both males and females ($p < 0.001$). Following the training period, there was a statistically significant increase in the PI_{max} in the training group. This increase was associated with a significant increase in the PIF. All patients overcame the minimal threshold PIF following the training. ***Conclusions:*** Some patients with severe COPD are not able to generate adequate flow to secure optimal lung deposition of the inhalation with the Turbuhaler. SIMT improves inspiratory muscle strength as well as PIF. Following 8 weeks of training, the optimal PIF enabling adequate lung deposition of the drug was attained in all the trained patients.

Introduction

Glucocorticosteroid and bronchodilator therapy with dry powder inhalers (DPI) is increasingly used in patients with chronic obstructive pulmonary disease (COPD) [1, 2]. It has already been shown that instructing the patient to take a 'forceful and deep' inhalation optimizes the use of DPIs [3].

In order to guarantee optimal lung deposition of the medication, it is necessary to generate a certain inspiratory flow through the inhaler. The degree of the optimal

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0025–7931/06/0732–0151$23.50/0

Accessible online at:
www.karger.com/res

Paltiel Weiner, MD
Department of Medicine A
Hillel Yaffe Medical Center
Hadera 38100 (Israel)
Tel. +972 46304527, Fax +972 46304522, E-Mail weiner@hillel-yaffe.health.gov.il

Table 1. Characteristics of the patients with COPD (first stage)

	Mild (n = 10)		Moderate (n = 10)		Severe (n = 10)	
	male	female	male	female	male	female
Age, years	63.3 ± 2.9	61.1 ± 2.8	64.6 ± 3.0	63.7 ± 2.8	65.2 ± 3.2	66.3 ± 3.0
BMI, kg/m^2	32.7 ± 2.1	30.6 ± 2.0	28.6 ± 2.0	29.7 ± 2.2	26.4 ± 2.0	27.4 ± 1.9
FVC, liters	3.0 ± 0.9	2.1 ± 0.8	2.8 ± 0.8	1.9 ± 0.7	2.6 ± 0.8	1.8 ± 0.7
% predicted	79 ± 3.2	84 ± 3.2	73 ± 3.3	74 ± 3.0	71 ± 2.9	69 ± 3.0
FEV_1, liters	2.2 ± 0.6	1.6 ± 0.6	1.9 ± 0.7	1.3 ± 0.6	1.1 ± 0.4	0.8 ± 0.5
% predicted	74 ± 2.9	76 ± 2.8	63 ± 2.6	62 ± 2.7	38 ± 1.8	36 ± 1.7
PI_{max}, cm H_2O	78 ± 2.1	70 ± 2.0	69 ± 2.2	58 ± 2.0	59 ± 1.9	48 ± 1.7
PIF, l/min						
Diskus	96 ± 4.4	81 ± 4.2	84 ± 4.3	73 ± 3.0	77 ± 3.1	66 ± 2.6
Turbuhaler	81 ± 4.0	70 ± 2.1	73 ± 3.6	66 ± 2.6	62 ± 1.9	54 ± 2.8
Medication						
Inhaled steroids, %	80	70	80	90	100	70
Bronchodilators, %	100	100	80	100	90	90
Theophylline, %	20	0	10	0	20	0

Values are expressed as means ± SEM. BMI = Body mass index.

flow depends on the internal airflow resistance of the various DPIs [4]. Using the Diskus of GlaxoSmithKline (Glaxo Wellcome Operations, UK), for example, an inspiratory flow of 30 l/min is enough for an optimal deposition of the drug in the patient's lung, while an inspiratory flow of 60 l/min is necessary to guarantee optimal deposition with the Turbuhaler of AstraZeneca (AstraZeneca AB, Sweden) [4, 5].

Patients with significant COPD have respiratory and peripheral muscle weakness [6, 7]. This weakness of the inspiratory muscles may cause a decrease in the ability of the patient to generate the optimal flow when using a DPI. In these patients, it is essential to measure the peak inspiratory flow (PIF) to optimize the inhalation therapy. Recently, a hand-held PIF meter has been developed (In-Check DIAL®; Clement Clarke International, Harlow, UK) that is able to mimic the internal resistance of several inhalers. In this way, it is possible to check whether the patient is able to generate a PIF that will lead to adequate lung deposition of the drug [8].

The purpose of the present study was to investigate the PIFs that patients with COPD can generate breathing through the two most popular DPIs in Israel, the Diskus and the Turbuhaler. In addition, we investigated whether in patients with low PIF specific inspiratory muscle training (SIMT) for 8 weeks will increase the PIF and overcome the minimal PIF necessary to guarantee optimal lung deposition.

Patients and Methods

Patients

Sixty patients with forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <70% of the predicted value and a diagnosis of COPD according to the criteria of the American Thoracic Society [9] were recruited for the first stage of the study. The study comprised 10 men and 10 women with spirometric evidence of mild chronic air flow limitation (FEV_1 >70% predicted), 10 men and 10 women with spirometric evidence of moderate chronic air flow limitation (FEV_1 = 50–70% of predicted), and 10 men and 10 women with spirometric evidence of severe chronic air flow limitation (FEV_1 <50% of predicted). We preferred to adopt the grading of COPD patients according to Siafakas et al. [10] over other grading systems because acute exacerbation of symptoms, which have an impact on a patient's quality of life and prognosis, are especially seen in patients with FEV_1 <50% of predicted. All COPD patients were in a stable clinical and functional status and received glucocorticosteroids using either Diskus or Turbuhaler. Their characteristics are summarized in table 1.

Twenty-eight patients, 16 men and 12 women, in a stable clinical and functional status were recruited for the second stage of the study. Inclusion criteria were spirometric evidence of severe chronic air flow limitation (FEV_1 <50% of predicted) and FEV_1/FVC <70% of predicted, with PIF being measured with the In-Check DIAL, with internal resistance of the Turbuhaler being <60 l/min. Of the 11 patients from the first stage of the study that were also suitable for the second stage, 6 (2 males and 4 females) were included in the second stage, 1 was abroad, 2 had exacerbation at the recruitment period, and 3 refused to continue the study. The characteristics of the patients included in the second stage of the study are summarized in table 2. Pharmacological treatment was not changed during the training period.

Table 2. Characteristics of the patients with COPD (second stage)

	Training group		Control group	
	male (n = 8)	female (n = 6)	male (n = 8)	female (n = 6)
Age, years	63.7 ± 3.0	62.1 ± 2.9	64.2 ± 3.0	60.7 ± 2.6
BMI, kg/m^2	27.9 ± 2.3	28.3 ± 2.1	27.4 ± 2.1	29.0 ± 2.4
FVC, liters	2.6 ± 0.7	1.8 ± 0.6	2.4 ± 0.8	2.0 ± 0.6
% predicted	71 ± 3.2	69 ± 3.2	73 ± 3.3	70 ± 3.0
FEV_1, liters	1.2 ± 0.4	0.9 ± 0.2	1.4 ± 0.4	1.1 ± 0.2
% predicted	37 ± 2.1	36 ± 1.9	39 ± 2.3	36 ± 1.9
PI_{max}, cm H_2O				
Before training	49 ± 1.9	42 ± 1.7	53 ± 1.9	47 ± 1.8
After training	61 ± 2.1[a]	55 ± 1.9[a]	53 ± 2.3	49 ± 1.9
Medication				
Inhaled steroids, %	86	93	100	93
Bronchodilators, %	100	100	93	100
Theophylline, %	21	7	7	0

Values are expressed as means ± SEM. BMI = Body mass index.
[a] Statistically significant values.

Tests

All tests were performed twice on 2 consecutive days for the first stage of the study, and before SIMT and within 1 week after the completion of the training period in the second stage of the study.

Peak Inspiratory Flow. PIF was measured using the In-Check DIAL. Patients inhaled through the device set for both Diskus and Turbuhaler resistances in a randomized manner on 2 consecutive days. For each resistance, three attempts were measured each day, and the highest value of six attempts was recorded for each resistance.

Spirometry. FVC and FEV_1 were measured three times each day on a computerized spirometer (Compact, Vitalograph, Buckingham, UK), and the best trial was reported.

Inspiratory Muscle Strength. Inspiratory muscle strength was assessed by measuring the maximal inspiratory mouth pressure (PI_{max}) at residual volume, as described previously by Black and Hyatt [11].

Mouth pressures were measured with a vacuumed 1,002 mouthpiece (VacuMed, Ventura, Calif., USA), with a small air leak to prevent pressure generation by glottis closure, connected to a pressure transducer and recorded on a strip chart recorder. The value obtained from the best of at least three efforts each day was used.

Training Protocol

The patients were randomized to one of two groups: 14 patients were assigned to receive SIMT, and 14 patients comprised the control group receiving training with very low load. All the data were collected by the same investigator who was blinded to the training group, and the patients were blinded to the mode of treatment. All subjects trained daily, six times a week, each session consisting of 1 h, for 8 weeks. The training was performed using an inspiratory muscle trainer (POWERbreathe®; Gaiam, Southam, UK). The subjects in the SIMT group started breathing at a resistance equal to 15% of their PI_{max} for 1 week. The resistance was then increased incrementally (5–10% each session), to reach 60% of their PI_{max} at the end of the 1st month. SIMT was then continued at 60% of their PI_{max} adjusted weekly to the new PI_{max} achieved. The control group trained with 'low load' (fixed resistance of 7 cm H_2O).

The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all the patients.

Data Analysis

The results are expressed as means ± SEM. Correlations were assessed by calculating Spearman's correlation coefficients. Comparisons of lung function, PIF, and the inspiratory muscle strength between the groups were carried out using the t test. A p value <0.05 was considered significant.

Results

First Stage

For patients with mild COPD, the mean PIFs using the Diskus were 96 ± 4.4 and 81 ± 4.2 l/min for males and females, respectively, 84 ± 4.3 and 73 ± 3.0 l/min for male and female patients with moderate COPD, and 77 ± 3.1 and 66 ± 2.6 l/min for male and female patients with severe COPD, respectively. Using the Turbuhaler, mean PIFs were 81 ± 4.0 and 70 ± 2.1, 73 ± 3.6 and 66 ± 2.6 and 62 ± 1.9 and 54 ± 2.8 l/min for male and female patients with mild, moderate and severe COPD, respectively (table 1).

The mean PIFs were significantly higher ($p < 0.005$) with the Diskus than with the Turbuhaler for all patient

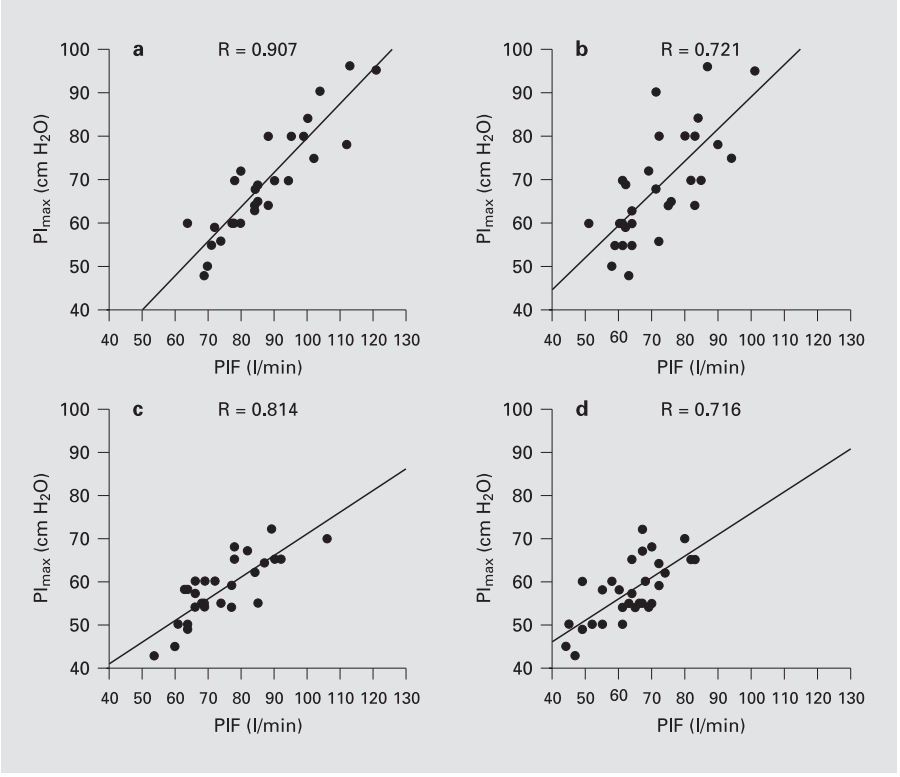

Fig. 1. Correlation between the PI_{max} and the PIF with the Diskus (**a**, **c**) and the Turbuhaler (**b**, **d**) in males (**a**, **b**) and females (**c**, **d**).

groups. All patients achieved the required minimum flow of 30 l/min with the Diskus. However, with the Turbuhaler, 12 patients (20%) could not generate the optimal flow of 60 l/min: 3 males with severe COPD and 9 females (7 with severe and 2 with moderate COPD).

PIF correlated very well with PI_{max} for the Diskus and the Turbuhaler, as well as for both males and females ($p < 0.001$; fig. 1). Body mass index was almost unchanged during the treatment period.

Second Stage

Baseline lung function characteristics and the inspiratory muscle strength of the patients with severe COPD are presented in table 2. There was no significant difference in the PI_{max} between the two groups (mean PI_{max} was 46.1 ± 1.8 cm H_2O in the training group and 49.7 ± 1.9 cm H_2O in the control group).

Baseline mean PIFs were significantly lower with the Turbuhaler (51.8 ± 3.1 l/min) than with the Diskus (63.8 ± 3.0 l/min, $p < 0.005$) and in the females (49.6 ± 2.8 vs. 54.2 ± 2.9 for the Turbuhaler and 59.9 ± 2.7 vs. 67.1 ± 3.2 l/min for the Diskus, $p < 0.001$).

Following the training period, there was a statistically significant increase in the PI_{max} in the training group (from 46.1 ± 1.8 to 58.7 ± 2.1 cm H_2O, $p < 0.001$) but not in the control group (table 2). This increase was associated with a significant increase in PIF. Using the Diskus, PIF increased from 64.8 ± 3.2 to 79.1 ± 3.6 l/min ($p < 0.001$) and using the Turbuhaler from 53.8 ± 3.0 to 68.6 ± 3.2 ($p < 0.001$) in the training group but not in the control group (table 3). All patients surpassed the minimal threshold PIF for the Turbuhaler following the training.

There was a very close correlation between the individual increase in PI_{max} and the individual increase in PIF using the Turbuhaler ($R = 0.836$, $p < 0.001$; fig. 2).

Discussion

In the present study, we have shown that some patients with severe COPD are not able to generate adequate flow to secure optimal lung deposition of the inhalation with one of the most popular inhalation devices. These patients were mainly females and had a low PI_{max}. Follow-

Table 3. PIFs of the patients with COPD (second stage)

	Diskus		Turbuhaler	
	training group	control group	training group	control group
PIF, l/min				
Before training	64.8 ± 3.2	62.5 ± 3.0	53.8 ± 3.0	48. ± 2.66
After training	79.1 ± 3.6[a]	63.2 ± 2.6	68.6 ± 3.2[a]	49.9 ± 2.8

Values are expressed as means ± SEM.
[a] Statistically significant.

ing SIMT, there was a significant increase in the PIFs of all patients, an increase that correlated well with the increase in inspiratory muscle strength.

In addition to the commonly used DPIs like the Turbuhaler and Diskus, there are numerous inhalation devices available on the market [12, 13], and the prescription of the most appropriate device to each patient is sometimes difficult. The internal airflow resistance and the ability of the patient to overcome it and to create an optimal inspiratory flow are among the criteria for choosing a specific device. The In-Check Dial has been recently introduced and by reproducing the resistance of several commonly used devices allows us to measure the inspiratory effort of patients using one of the various devices. This is most important when evaluating children with asthma and COPD patients [14, 15].

It has been shown previously that pulmonary bioavailability is predictive of the overall clinical effect of inhaled drugs [16]. Lung deposition of the inhaled medication with the Diskus is optimal and constant from 30 to 90 l/min, while it is optimal at a flow >60 l/min with the Turbuhaler [4, 17, 18]. The maximal inspiratory flow, at a given volume, depends on the airway caliber as well as the strength and speed of shortening of the inspiratory muscles [19]. In our study, a close correlation was found between the PIF and the inspiratory muscle strength assessed by the PI_{max}, indicating a role of muscle force in generating inspiratory flow.

Inspiratory muscle weakness is found in the majority of patients with significant COPD [20]. Patients with COPD must breathe at high lung volumes to maintain patency of their narrowed airways. The major abnormality of respiratory muscle function in these patients is thought to be the mechanical disadvantage caused by this hyperinflation. Hyperinflation depresses the dome of the diaphragm, shortens its fibers, and forces it to work on an ineffective portion of its length-tension curve [21].

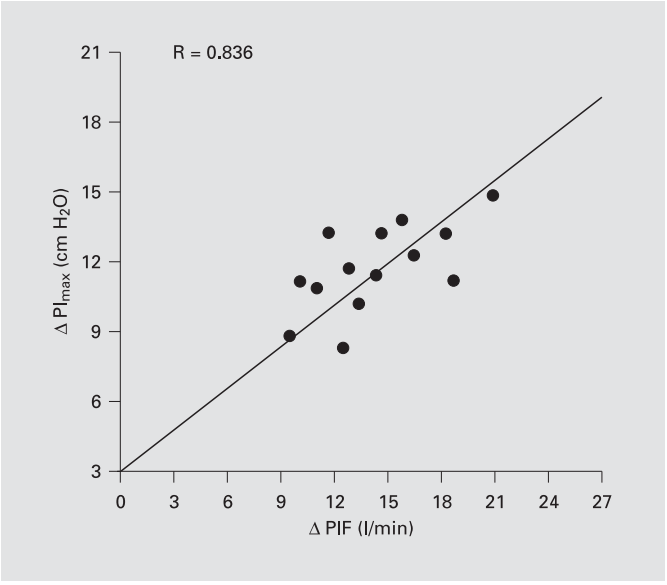

Fig. 2. Correlation between the increase in PI_{max} and the increase in PIF with the Diskus and the Turbuhaler in patients with severe COPD following the training period.

In the present study, all patients were encouraged to do their utmost. Probably, a larger percentage of patients will not inhale optimally at home. Previously, it has been shown that during comfortable inhalation, the PIF values were lower in about 40% [22], indicating that more patients will probably not inhale the adequate amount of the drug at home.

Inspiratory muscle training has been extensively investigated in patients with COPD. It has been shown that when the training stimulus was adequate, there was a significant increase in the inspiratory muscle strength, and in most COPD patients, dyspnea and functional exercise

capacity improved as a result of such training [23–25]. In our training group, that has been trained with significant loads, all participants increased significantly their inspiratory muscle strength. It is not surprising, therefore, that PIF, which is partially depending on the strength and speed of shortening of the inspiratory muscles, improved with increasing inspiratory muscle strength.

In conclusion, the present study shows that in patients with moderate-severe COPD, mainly in females, when choosing the appropriate inhaler, the resistance of the device should be weighed against the patient's inspiratory muscle strength and his/her ability to generate the required flow to attain adequate lung deposition of the drug. Patients that are unable to generate the required flow with the Turbuhaler should be treated with the Diskus, with which a smaller flow is required. The assessment can be performed with the In-Check DIAL. In addition, SIMT, which improves inspiratory muscle strength as well as PIF, should be incorporated in the rehabilitation program for patients with severe COPD who are unable to generate the flow required for adequate lung deposition of the drug. Following 8 weeks of training, all of our trained patients surpassed the optimal PIF that allows adequate lung deposition of the drug.

References

1 Calverley P, Pauwels R, Vestbo J, et al: Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449–456.

2 van Beurden WJ, Harff GA, Dekhuijzen PN, van der Poel-Smet SM, Smeenk FW: Effects of inhaled corticosteroids with different lung deposition on exhaled hydrogen peroxide in stable COPD patients. Respiration 2003;70:242–248.

3 Persson G, Olsson B, Soliman S: The impact of inspiratory effort on inspiratory flow through Turbuhaler in asthmatic patients. Eur Respir J 1997;10:681–684.

4 De Boer AH, Gjaltema D, Hagedoorn P: Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers. 2. Effect of peak flow rate (PIFR) and inspiration time on the in vitro drug release from three different types of commercial dry powder inhalers. Int J Pharm 1996;138:45–56.

5 Engel T, Heinig JH, Madsen F, Nikander K: Peak inspiratory flow and inspiratory vital capacity of patients with asthma measured with and without a new dry-powder inhaler device (Turbuhaler). Eur Respir J 1990;3:1037–1041.

6 Gosselink R, Troosters T, Decramer M: Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2000;20:353–360.

7 Rochester DF, Braun NT: Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis 1985;132:42–47.

8 Van Der Palen J: Peak inspiratory flow through Diskus and Turbuhaler, measured by means of a peak inspiratory flow meter (In-Check DIAL). Respir Med 2003;97:285–289.

9 American Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (review). Am J Respir Crit Care Med 1995;152:S77–S121.

10 Siafakas NM, Vermeire P, Pride NB, et al: Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398–1420.

11 Black LF, Hyatt RE: Maximal respiratory pressures: normal values and the relationship to age and sex. Am Rev Respir Dis 1969;99:696–702.

12 Kunkel G, Schaper C, Noga O, et al: Efficacy, safety, and acceptance of beclomethasone dipropionate administered via a new dry powder inhaler or a standard CFC metered-dose inhaler in asthma patients. Respiration 2003;70:399–406.

13 Dahl R, Creemers JP, Van Noord J, et al: Comparable efficacy and tolerability of formoterol (Foradil) administered via a novel multi-dose dry powder inhaler (Certihaler™) or the Aerolizer® dry powder inhaler in patients with persistent asthma. Respiration 2004;71:126–133.

14 Nsour WM, Alldred A, Corrado J, Chrystyn H: Measurement of peak inhalation rates with an In-Check Meter to identify an elderly patient's ability to use a Turbuhaler. Respir Med 2001;95:965–968.

15 Brazhnik VA, Sakharova GM, Makretskaia ON: The role of inspiratory flow measurement in choosing a suitable device in asthmatic patients Eur Respir J 2000;16(suppl 31):316s.

16 Derom E, Borgstrom L, Van Schoor J, Lofroos AB, Pauwels R: Lung deposition and protective effect of terbutaline delivered from pressurized metered-dose inhalers and the Turbuhaler in asthmatic individuals. Am J Respir Crit Care Med 2001;164:1398–1402.

17 Borgstrom L, Bondesson E, Moren F, Trofast E, Newman SP: Lung deposition of budesonide inhaled via Turbuhaler: A comparison with terbutaline sulphate in normal subjects. Eur Respir J 1994;7:69–73.

18 Hill LS, Slater AL: A comparison of the performance of two modern multidose dry powder asthma inhalers. Respir Med 1998;92:105–110.

19 Fry DL, Hyatt RE: Pulmonary mechanics: a unified analysis of the relationship between pressure, volume and gas flow in the lungs of normal and diseased human subjects. Am J Med 1960;29:-672–689.

20 Rochester DF, Braun NM, Arora NS: Respiratory muscle strength in chronic obstructive pulmonary disease. Am Rev Respir Dis 1979;119:151–154.

21 Luce JM, Culver BH: Respiratory muscle function in health and disease. Chest 1982;81:82–90.

22 De Boer AH, Winter HMI, Lerk CF: Inhalation characteristics and their effects on in vitro drug delivery from dry powders inhalers. 1. Inhalation characteristics, work of breathing and volunteer's preference in dependence of the inhaler resistance. Int J Pharm 1996;130:231–244.

23 Weiner P, Magadle R, Berar-Yanay N, Davidovich A, Weiner M: The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD. Chest 2000;118:672–678.

24 Hernandez MT, Rubio TM, Ruiz FO, Riera HS, Gil RS, Gomez JC: Results of a home-based training program for patients with COPD. Chest 2000;118:106–114.

25 Kim A, Larsen J, Covey M, Vitalo CA, Alex CG, Patel M: Inspiratory muscle training in patients with chronic obstructive pulmonary disease. Nurs Res 1993;42:356–362.