

# Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters

L Pekka Malmberg<sup>1</sup>  
Paula Ryttilä<sup>2</sup>  
Pertti Happonen<sup>2</sup>  
Tari Haahtela<sup>1</sup>

<sup>1</sup>Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland; <sup>2</sup>Orion Corporation, Orion Pharma, Espoo, Finland

**Background:** Dry powder inhalers (DPIs) are inspiratory flow driven and hence flow dependent. Most patients with chronic obstructive pulmonary disease (COPD) are elderly and have poor lung function. The factors affecting their inspiratory flows through inhalers are unclear.

**Objective:** To study peak inspiratory flows (PIFs) and their determinants through a DPI in COPD patients of varying age and severity.

**Methods:** Flow-volume spirometry was performed in 93 COPD patients. Maximum PIF rates were recorded through an empty Easyhaler® (PIF<sub>EH</sub>; Orion Corporation, Espoo, Finland), a DPI that provides consistent dose delivery at inhalation rates through the inhaler of 28 L/min or higher.

**Results:** The mean PIF<sub>EH</sub> was 54 L/min (range 26–95 L/min) with a coefficient of variation of 7%. All but two patients were able to generate a flow of  $\geq 28$  L/min. In a general linear model, the independent determinants for PIF<sub>EH</sub> were age ( $P = 0.02$ ) and gender ( $P = 0.01$ ), and forced expiratory volume in 1 s (FEV<sub>1</sub>) expressed as percent predicted was not a significant factor. The regression model accounted only for 18% of the variation in PIF<sub>EH</sub>.

**Conclusion:** In patients with COPD, age and gender are more important determinants of inspiratory flow through DPIs than the degree of expiratory airway obstruction. Most COPD patients with varying age and severity are able to generate inspiratory flows through the test inhaler that is sufficient for optimal drug delivery to the lower airways.

**Keywords:** COPD, forced expiratory volume, peak inspiratory flow

## Introduction

Chronic obstructive pulmonary disease (COPD) represents a global burden with increasing prevalence, morbidity, and mortality.<sup>1</sup> Patients with diagnosed COPD are preferably treated with inhaled medications on a regular daily basis.<sup>1</sup> Adherence and the correct use of an inhaler are important for successful treatment.<sup>2</sup> Inability to use the inhaler correctly may result in failure to get the intended dose of medication to the airways. Therefore, knowledge of the requirements for specific inhalers is necessary when prescribing inhalation therapy.

The choice of the inhaler device is an important part of the management of patients with COPD. Two types of portable inhalers are available: pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPI). DPIs are inspiratory flow driven and easier to use compared with pMDIs as no coordination is required between actuation and inhalation. In contrast to MDIs, DPIs have varying internal resistances, require sufficient inspiratory flows, and are consequently dependent, in various degrees, on the inspiratory effort of the patient.<sup>3,4</sup> Easyhaler® (Orion Corporation, Espoo, Finland) is a

Correspondence: L Pekka Malmberg  
Unit of Clinical Physiology, Skin and Allergy Hospital, Helsinki University Central Hospital, PO Box 160, FIN 00029 Helsinki, Finland  
Tel +358-9-471-86217  
Fax +358-9-471 86280  
Email pekka.malmberg@hus.fi

device-metered DPI with a relatively high internal resistance. *In vitro* tests have shown that the dose delivery is consistent and accurate starting from a minimum inspiratory flow of 28 L/min through the inhaler.<sup>5,6</sup> Easyhaler containing salbutamol, formoterol, budesonide, or beclometasone dipropionate is marketed in a number of countries, drug substances that are often prescribed for patients with COPD.

A few studies have assessed the ability of patients with COPD to use various inhaler devices.<sup>7–10</sup> It appears that patients with severe COPD may have problems in achieving the minimum required inspiratory flow rate through DPIs to get the dose to the airways.<sup>8</sup> Many patients with COPD are also elderly and may have muscle fatigue. Regardless of the absence or presence of disease, a study in the elderly showed that their ability to generate sufficiently high inspiratory flows through DPIs was clearly compromised.<sup>9</sup> The main factors that affect inspiratory flows through inhalers in patients with COPD, and whether any subgroups not capable of efficient use of specific DPIs could be identified are unclear.

The aim of this study was to investigate the peak inspiratory flow through the Easyhaler (PIF<sub>EH</sub>) inhaler in patients with COPD of various degrees of airway obstruction in order to assess the ability of the patients to effectively use the device, and to investigate the determinants of the PIF<sub>EH</sub>, using other lung function variables and demographic factors of the patients as explanatory variables.

## Materials and methods

A total of 104 consecutive patients with previously diagnosed COPD treated at the Skin and Allergy Hospital, Helsinki University Central Hospital, were invited to take part in the study. A total of 93 patients gave their written informed consent. Patients with a current COPD exacerbation were not allowed to participate. The patients were allowed to use their regular medication on the day of the test. All patients had typical respiratory symptoms and fulfilled the physiological criterion for COPD with a postbronchodilator forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity ratio of less than 70%.<sup>1</sup> The majority of patients were current or exsmokers. The demography and baseline characteristics of the patients are shown in Table 1. The study protocol was investigator-initiated and approved by the Ethics committee of the Department of Medicine of the Helsinki University Central Hospital.

Flow-volume spirometry was performed according to ATS/ERS guidelines<sup>11</sup> including the recording of native peak inspiratory flow (PIF) rate. Maximum PIF rates were recorded through an empty Easyhaler (PIF<sub>EH</sub>) connected

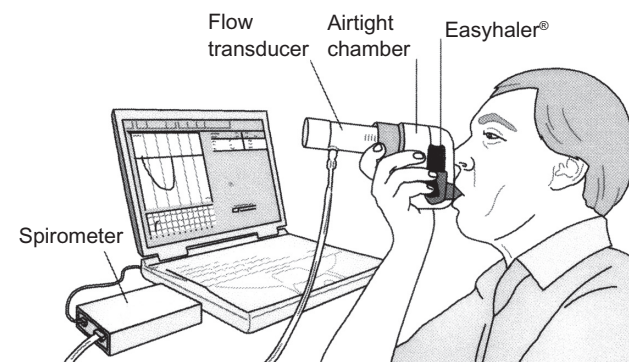
**Table 1** Demography and baseline characteristics of the patients

Variable	Result
Number of patients	93
Sex (female/male)	44/49
Mean age, years (range)	65 (47–84)
Smoking history	
Current smokers	48
Exsmokers	44
Nonsmokers	1
Mean pack years (range)	40 (0–110)
FEV <sub>1</sub> , L (range)	1.5 (0.49–3.30)
FEV <sub>1</sub> , percent predicted normal (range)	51 (18–96)
FVC, L (range)	3.0 (1.4–5.9)
FVC, percent predicted normal (range)	81 (37–130)
FEV <sub>1</sub> /FVC (%)	44 (21–69)
Current medication, number of patients (%)	
Inhaled corticosteroids	89 (96)
Long-acting $\beta_2$ -agonist	68 (73)
Short-acting $\beta_2$ -agonist	63 (68)
Anticholinergic	60 (65)
Theophylline	22 (24)

**Abbreviations:** FEV, forced expiratory volume; FVC, forced vital capacity.

to a pneumotachograph (Spiromaster MX, Medikro Ltd, Kuopio, Finland; Figure 1). The patients were instructed to exhale gently (to functional residual capacity) and then to inhale as fast and long as possible through the inhaler. They practiced this inhalation maneuver three times and thereafter three PIF<sub>EH</sub> measurements were recorded consecutively. Spirometry and PIF<sub>EH</sub> measurements were performed in random order to compensate for the possible confounding effect of muscle fatigue.

The primary outcome variable of the study was PIF<sub>EH</sub>. The proportion of patients with PIF<sub>EH</sub> exceeding the minimum flow of 28 L/min for effective use of Easyhaler was calculated. The reproducibility of PIF<sub>EH</sub> was estimated with an analysis of variance. General linear models were used to investigate independent determinants of PIF<sub>EH</sub> and their regression coefficients, in a linear model of  $PIF_{EH} = b_0 + b_1x_1 + b_2x_2 + \dots$



**Figure 1** The Easyhaler inhaler connected in series to a pneumotachograph.

$b_k x_k$ , where  $x_{1...k}$  are the independent variables and  $b_{1...k}$  are their coefficients.

## Results

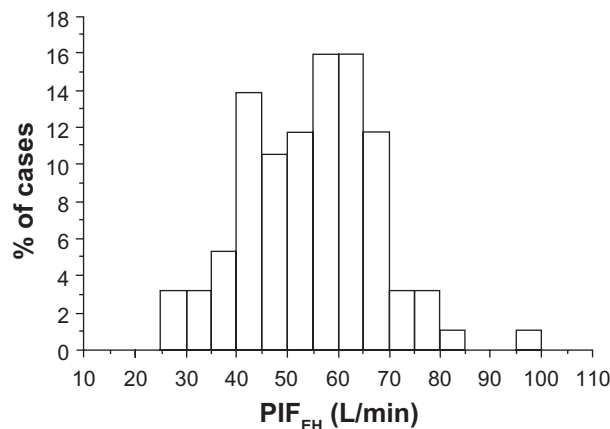
The mean PIF<sub>EH</sub> was 54 L/min (range 26–95 L/min) with a within-subject coefficient of variation of 7.4% (range 0.9%–40.7%) in three consecutive inhalations. Ninety-one of the 93 patients (98%) could generate a PIF<sub>EH</sub>  $\geq$  28 L/min and a total of 271 inspiratory maneuvers through the inhaler out of 279 recorded (97%) showed flow rates  $\geq$  28 L/min. The distribution of the PIF<sub>EH</sub> rates is shown in Figure 2.

The relationships between PIF<sub>EH</sub> and lung function data and the patients' age, height, and weight are shown in Table 2. The native PIF had the strongest association with PIF<sub>EH</sub> both in terms of absolute values (L/min) and percent predicted normal values ( $r = 0.54$ ;  $P < 0.0001$  and  $r = 0.37$ ;  $P = 0.0003$ , respectively).

The relationship between PIF<sub>EH</sub> and the patients' age (males and females marked separately) is shown in Figure 3. A significant correlation was seen between age and PIF<sub>EH</sub> ( $P = 0.004$ ). Women had significantly lower PIF<sub>EH</sub> ( $P = 0.004$ ) than men. PIF<sub>EH</sub> was also significantly related to height and weight although the correlation coefficients were small.

The univariate relationships of PIF<sub>EH</sub> with FEV<sub>1</sub> and peak expiratory flow rates were statistically significant ( $r = 0.30$ ;  $P = 0.004$  and  $r = 0.32$ ;  $P = 0.02$ , respectively). However, FEV<sub>1</sub> as percent of predicted normal values, ie, FEV<sub>1</sub> adjusted for age, gender, and height of the subject, was not significantly related to PIF<sub>EH</sub> as shown in Figure 4.

To construct a model predicting PIF<sub>EH</sub>, a set of explanatory variables were introduced stepwise. Since all



**Figure 2** The distribution of the peak inspiratory flow through Easyhaler (PIF<sub>EH</sub>) in COPD patients of varying severity ( $n = 93$ ).

**Table 2** The relationship between peak inspiratory flow through Easyhaler and age, height, weight, and lung function in 93 COPD patients

Variable	$r^a$	$P$
Age, years	-0.30	0.004
Height, cm	0.26	0.01
Weight, Kg	0.22	0.03
FEV <sub>1</sub> , L	0.30	0.004
FEV <sub>1</sub> , percent predicted	0.11	0.28
PEF, L/s	0.32	0.002
PEF, percent predicted	0.17	0.11
PIF, L/s	0.54	<0.0001
PIF, percent predicted	0.37	0.0003

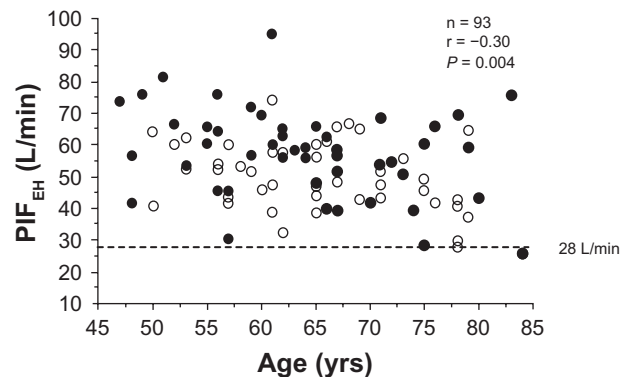
**Notes:** <sup>a</sup>Correlation coefficient (Pearson).

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 s; PEF, peak expiratory flow; PIF, peak inspiratory flow.

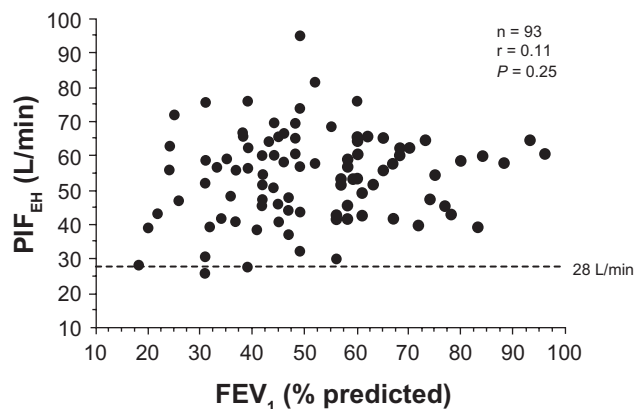
lung function variables showed considerable collinearity with their relationship to PIF<sub>EH</sub>, FEV<sub>1</sub> as percent predicted was chosen to represent the level of lung function impairment in the model. Table 3 shows the results of the linear regression model for best prediction of PIF<sub>EH</sub> values. Age and gender were significant predictors of the PIF through the inhaler. Other variables introduced to the model thereafter, such as FEV<sub>1</sub>, height, and weight, had insignificant effects. The full model, however, explained only 18% of the variation in PIF<sub>EH</sub>.

## Discussion

Our study found that almost all patients with COPD (91 of 93 patients) have an inspiratory effort sufficient to generate inspiratory flows through the test inhaler that should result in therapeutic benefit with a drug-loaded device. The series of patients represented a wide variety of disease severity and airway obstruction and the results are, therefore, applicable to most patients with COPD.



**Figure 3** The relationship between peak inspiratory flow through Easyhaler (PIF<sub>EH</sub>) and age in COPD patients of varying severity ( $n = 93$ ). Closed circles = men; open circles = women.



**Figure 4** The relationship between peak inspiratory flow through Easyhaler ( $PIF_{EH}$ ) and  $FEV_1$  percent predicted in COPD patients ( $n = 93$ ).

Previously, data on inspiratory flow characteristics through DPIs in COPD patients have been limited. A study using Turbuhaler<sup>®7</sup> showed that all COPD patients were able to generate PIF through the inhaler of 28 L/min, with a variation similar to that we found (Figure 2). However, *in vitro* tests suggest that optimal dosing with this inhaler (Turbuhaler) would require flows of at least 40–60 L/min.<sup>6,12</sup> Although PIF through the inhaler showed significant associations with  $FEV_1$  in liters and native PIF, this study was not aimed to investigate the effect of degree of lung function impairment (expressed as  $FEV_1$  percent predicted) or other factors such as age or gender. In an other study by Broeders et al<sup>8</sup> the inhalation profiles through Turbuhaler and Diskus<sup>®</sup> inhalers were compared in asthmatics and COPD patients. In the severe COPD group, 7%–19% of the patients showed suboptimal flows through the inhalers. They found that PIF through the inhaler correlated with other parameters of inspiratory capacity like native PIF or maximal inspiratory pressures, which is in agreement with our results. However, the effect

**Table 3** Results of the general linear model<sup>a</sup> to predict  $PIF_{EH}$  in 93 patients with COPD. For the full model,  $r^2 = 0.18$  ( $P = 0.0014$ )

Parameter	Coefficient	Standard error	P
Intercept	71.7	13.0	<0.0001
Age, years	-0.34	0.15	0.022
Gender			
female	-6.89	2.62	0.010
male	0.00		
$FEV_1$ , percent predicted	0.089	0.077	0.25
Weight, kg	0.047	0.058	0.42

**Notes:** <sup>a</sup> $y = b_0 + b_1x_1 + b_2x_2 + \dots + b_kx_k$ , where  $x_{1..k}$  are the explanatory parameters and  $b_{1..k}$  are their regression coefficients; see text for an example.

**Abbreviations:**  $FEV_1$ , forced expiratory volume in 1 s;  $PIF_{EH}$ , peak inspiratory flow through the easyhaler.

of other factors such as age or sex were not included in their analyses. Janssens et al<sup>9</sup> studied inspiratory flow rates at different levels of resistance, corresponding to different types of DPIs, in elderly COPD patients. This study showed that in elderly patients, the ability to generate sufficient inspiratory flows across a DPI is compromised, but since only patients over 70 years were included, it is difficult to draw any conclusions whether age, the degree of airway obstruction, or other mechanisms are the main determinants for the inspiratory flows. The current study is the first specifically designed to clarify the relative impact of these factors, as well as the performance of Easyhaler in patients with COPD.

The present study included only patients with stable disease, and thus the results may be questioned when the inhaler has to be used in situations perceived as constrained.<sup>13</sup> Such situations include worsening of asthma, severe COPD in general, and COPD exacerbations. Even though exhalation may be severely affected in these conditions, it is known that inspiration is much less so.<sup>14</sup> A study of the course of inhalation profiles during an exacerbation of obstructive lung disease also showed that despite minor reductions in PIF during the acute phase, all patients were able to generate flows of 30 L/min or more through the DPIs.<sup>15</sup> A study investigating patients with COPD of various degrees of airway obstruction did not find differences in lung deposition between subjects with mild or more severe airway obstruction.<sup>16</sup> The current study also included a wide variety of disease severity and airway obstruction, making the results more applicable to most patients with COPD.

It is generally believed that DPIs with low internal resistance are more suitable for patients with more severe airway obstruction. However, as the turbulent energy is a product of the flow and the inhaler's resistance, for a set energy level needed for de-aggregation of the drug particles, the flow required through a low resistance DPI will be higher than that of a high-resistance DPI.<sup>17</sup> With a high-resistance DPI, the inspiratory flow through the inhaler will be determined mostly by the inhaler's resistance and is less affected by varying airway resistance of the patient, which may result in a more consistent dose emission.<sup>18</sup> The Easyhaler is an example of an inhaler with a relatively high internal resistance and consistent dose delivery over a wide range of inspiratory flows.<sup>6</sup> The observed inspiratory flows observed in the current study (Figure 2) are well within these limits, so despite the high resistance of the inhaler, the great majority of COPD patients were able to achieve sufficient inspiratory flows through Easyhaler for optimal drug delivery to the lower

airways. This finding agrees with a previous study of young children with asthma who also showed sufficient inspiratory flows through this inhaler.<sup>19</sup> Furthermore, a study with pediatric and adult asthmatic patients has confirmed that clinical efficacy of salbutamol is maintained even at low inspiratory flow rates when using Easyhaler.<sup>20</sup>

In view of the previous literature, however, several potential factors may limit the ability of COPD patients to generate sufficient inspiratory flows through DPIs.<sup>8,9</sup> We found significant associations with age and gender (Figure 3) which have not been specifically reported earlier, although problems with inspiratory flows in elderly patients have been shown to be common.<sup>9</sup> The results in Figure 4 slightly contradict with those of Broeders et al<sup>8</sup> who found suboptimal inspiratory flows more common in severe COPD patients with a mean FEV<sub>1</sub> of 34% predicted. However, they did not analyze the effect of FEV<sub>1</sub> as a continuous variable as in the present study. We constructed a multivariate model to predict PIF<sub>EH</sub> to clarify these factors and their relative importance, and to better identify patients with increased risk of insufficient inspiratory flows through the DPI. Factors that are generally available when treating the patients, ie, age, gender, height, weight, and lung function, were entered into the regression analysis. According to the model (Table 3), as an example, a 70-year-old female patient with FEV<sub>1</sub> of 30% predicted and height of 160 cm should have PIF<sub>EH</sub> of  $71.7 - 0.34 \times 70 - 6.89 + 0.089 \times 30 + 0.047 \times 160 = 51.2$  L/min. The regression analysis showed that age and gender had independent effects on PIF<sub>EH</sub> and were more important than the degree of airway obstruction (expressed as FEV<sub>1</sub> percent predicted), which did not have a significant effect in the model. The low coefficient of determination suggests that additional physiological factors than those measured in this study should be considered to accurately predict PIF through inhalers. Such factors might include more direct measurements of inspiratory muscle performance or maximum inspiratory pressures.<sup>8</sup> However, such data are seldom available when treating patients in clinical practice. The coefficient of determination was also too low for our model to be useful for clinical purposes. Therefore, it is advisable to check PIFs through the inhaler individually,<sup>17</sup> especially in elderly patients with COPD, and whenever found unsatisfactory, alternative routes for drug administration should be considered, such as jet nebulizers or other flow-independent aerosol delivery systems.

The current results are mainly explained by the general physiological determinants of inspiratory flows. Maximum

inspiratory flows are dependent on the inspiratory pressure generated by the inspiratory muscles. Since during inspiration, pleural pressure is always subatmospheric and lower than bronchial pressure, airflow limitation does not occur, although increased airway resistance in patients with obstructive pulmonary diseases may have a minor effect on flow rates. Accordingly, maximum inspiratory flows in COPD patients are significantly less affected than expiratory flows.<sup>21</sup> Potential factors decreasing inspiratory muscle performance in COPD patients include aging,<sup>22</sup> malnutrition, and hyperinflation,<sup>23</sup> although in the latter factor, adaptive mechanisms may partly restore the force generating capacity of the respiratory muscles. The gender-related difference in maximum inspiratory flows has been previously shown in healthy subjects,<sup>22</sup> but not in patients with COPD or in relation to PIF through inhalers. This difference has been attributed to the overall better strength of the skeletal muscles in men, due to hormonal or genetic differences.<sup>22</sup>

## Conclusion

We conclude that age and gender in COPD patients are more important determinants of inspiratory flow through DPIs than the degree of expiratory airway obstruction. Most COPD patients with varying age and severity are able to generate inspiratory flows through Easyhaler that is sufficient for optimal drug delivery to the lower airways.

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## Disclosures

The authors report no conflicts of interest in this work. LPM has received fees for lectures in symposia sponsored by Astrazeneca, Glaxo Smith Kline, MSD, Orion Pharma and Schering Plough; PR is a full-time employee of Orion Pharma; PH is a full-time employee of Orion Pharma and holds stock in Orion Corporation; TH has received fees for lectures in symposia sponsored by Alk/Abello, AstraZeneca, Meda Oy, MSD and Orion Pharma.

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