ERJ Express. Published on September 26, 2007 as doi: 10.1183/09031936.00024807

Inspiratory flow rates at different levels of resistance in elderly COPD patients

Wim Janssens [1], Paul VandenBrande [1,2], Elke Hardeman [2], Ellen De Langhe [2], Tom Philps [2], Thierry Troosters [1], Marc Decramer [1]

1. Respiratory Division, University Hospital Katholieke Universiteit Leuven, Belgium
2. Respiratory Division, Hospital Sint-Maarten Duffel, Belgium

Corresponding author:
Wim Janssens, MD, PhD
Respiratory Division, University Hospital Gasthuisberg
Herestraat 49, 3000 Leuven
Belgium
Tel: +3216346800
Fax: +3216346803
Email: wim.janssens@uz.kuleuven.ac.be

Abstract

Dry powder inhalers (DPI) are increasingly replacing metered dose inhalers (MDI) in elderly COPD patients. Most of the DPIs, however, are dependent on inspiratory flow which is compromised by the ageing process itself. With the In-check DIAL method, we compared peak inspiratory flow rates (PIF) in elderly COPD patients (n=26) and matched control subjects (n=14) at a preset resistance level of the Aeroliser, the Diskus and the Turbuhaler. It was found that the PIF measured by the in-check method positively correlated with the PIF derived from spirometry, forced vital capacity and maximal inspiratory pressure, whilst a negative but significant correlation was observed with age. PIF derived from spirometry and age were independent variables which determined PIF across the device, whereas the presence or absence of COPD was not related. When comparing elderly COPD patients with matched elderly controls no difference could be found in PIFs at the different resistances. However, an important number of patients did not reach the recommended flow rate, especially when using the Turbuhaler (30%). In conclusion, this study demonstrates that in elderly patients the ability to generate sufficient inspiratory flow across a DPI is compromised, irrespective of the presence of COPD.

Keywords

Chronic obstructive pulmonary disease, Dry powder inhaler, Elderly, In-Check Dial, Peak **inspiratory** flow

Introduction

Inhaled medication plays an important role in the treatment of chronic obstructive pulmonary disease (COPD) and for some years dry powder inhalers (DPIs) are being increasingly replaced by metered dose inhalers (MDIs). DPIs are interesting since they do not require the need for coordinate actuation of the MDI device with inhalation or the use of a large spacer device [1-3]. Several DPIs are available for administrating inhaled corticosteroids (ICS) as well as bronchodilators, each of them corresponding to a different type of inhaler (e.g. Diskus®, Turbuhaler®, Aeroliser®,…). During the inspiratory effort the patient is generating a pressure drop with a consequent airflow across the DPI. This inspiratory flow has to be high enough to disaggregate and adequately disperse the drug powder into an aerosol cloud of drug particles and to guarantee an optimal deposition of the medication in the lung [3-5]. Such peak inspiratory flows (PIFs) are not only dependent on the patient's inhalation effort but also on the internal resistance of the device [6-8].

It has been shown that optimal deposition of medication with DPIs is not achieved in some patients with low inspiratory flow rates, such as children [9,10] or patients with asthma or COPD, especially during acute exacerbations [11-13]. In such conditions the use of a DPI with low internal resistance has been suggested, ensuring an optimal deposition despite the lower flow [12,14]. In addition, many clinicians are nowadays confronted with an important number of COPD patients who are older than 70 years. In this subpopulation DPIs are often preferred to MDIs because the coordination between device and inhalation becomes increasingly difficult with age [1,15,16]. However, elderly subjects are known to have reduced respiratory muscle strength and decreased PIF due to the ageing process itself, which may jeopardize the adequate use of DPI independently of COPD [17].

One recent publication reports about decreased inspiratory flow rates at high levels of resistance in elderly COPD patients [18]. In view of this perspective, we performed a study in which we measured PIF at different levels of resistance in elderly COPD patients and compared them with matched control subjects. We also evaluated whether elderly COPD patients could generate the required PIF to overcome the internal resistance of currently available DPIs.

Materials and methods

Study population:

All subjects (n =40) were males. The minimal age was 70 years, the oldest participant was 87 years. The elderly patients with COPD (n=26) were recruited from the outpatient clinic of pulmonary medicine of the Algemeen Ziekenhuis Sint Maarten, Duffel, Belgium. Diagnosis of COPD was based on a smoking history of minimum 10 pack years and the GOLD definition of FEV1/FVC < 70%. The elderly control group consisted of (n=14) subjects without COPD, who were community-dwelling and were recruited through the files of the local general practioners. Those subjects had a questionnaire and a clinical examination that proved a good general condition, without taking pulmonary medication and excluding any pulmonary complaint or disease. Ethics committee approval was obtained and all participants gave informed consent.

Pulmonary function measurements:

Pulmonary function variables were measured according to the European Respiratory Society guidelines for pulmonary function testing and the results were expressed as a percentage of the predicted normal values of Quanjer and colleagues [19]. MIP and MEP were measured according to a modification of the method of Black and Hyatt [20]. PImax was measured from residual volume and PEmax was measured as close as possible to total lung capacity (TLC). Pmax was defined as the highest pressure sustained for 1 second against a closed mouthpiece. COPD patients were asked to withhold from long-acting $ß_2$-agonists 12 hours prior to the lung function test as the corresponding devices were subject of this study. All measurements were performed between 9 and 11 am. All manoeuvres were executed and encouraged by trained technicians under the supervision of medical staff.

In-check Inhaler assessment:

PIF related to different resistances, was measured using the In-Check Inhaler Assessment Kit (Clement Clarke International Ltd, Harlow, UK) [6,14,21]. We used this device in order to compare peak inspiratory flow rates over three different DPIs that are commonly used in our country for the administration of long-acting ß$_2$-agonists. PIF device was defined as the maximal inspiratory flow over the device without additional resistance and compared with the maximal inspiratory flows over the device at a given resistance of 0.1 cmH_2O/L/min (Turbuhaler®), 0.086 cmH_2O/L/min (Diskus®) and 0.055 cmH_2O/L/min (Aeroliser®). The highest value of 3 attempts was recorded. PIFs above 60 L/min are generally believed to be the optimal flows for most of the devices, whilst PIFs below 30 L/min are accepted to be insufficient for generating any effect [6,22-30]. As there is still discussion about the effectiveness of PIFs ranging between 30 and 60 L/min [14,31,32], an arbitrary cut-off at a PIF of 45 L/min was made in order to distinguish therapeutic flows from sub-therapeutic levels.

Statistical analyses:

Data are expressed as mean ± SD. All statistical tests were performed with SAS software. Subjects's characteristics and lung function tests are compared by unpaired student's T-test. Correlations between different variables are expressed by Pearson correlation coefficients. A stepwise multiple regression is performed to investigate independent predictors of the peak inspiratory flow through the device at different resistances. Potentially important variables were FVC, FEV1, FVC %predicted, FEV1 %predicted, PIF, age, inspiratory muscle force, COPD diagnosis and severity of COPD. These variables were all included in the regression models in which the 0.05 significance level was retained for final entry. According to the GOLD classification, severity of COPD was introduced as a dichotomic variable, differentiating severe and very severe COPD (FEV1 %pred < 50%) from moderate and mild COPD. PIFs at different resistances were compared with one-way ANOVA. To compare PIFs at different resistances between COPD patients and elderly controls a two-sided ANOVA analysis was done. P-value of 0.05 was considered as significant.

Results

26 COPD patients and 14 controls were included the study. Table 1 demonstrates the baseline characteristics (mean ± SD) of both groups. To investigate which parameters may determine

the PIF as assessed by the In-Check dial, a correlation analysis was performed in the whole study population (n= 40) as well as in the COPD subgroup (n = 26) (Figure 1). In both groups PIF measured by the In-check method at zero resistance (PIF device) correlated best with the PIF measured during spirometry ($r = 0.51$, whole group and $r = 0.58$, COPD ; $p < 0.005$). In the total study group, PIF device also significantly ($p < 0.005$) correlated with age ($r = -0{,}5$), FVC(L) ($r = 0.46$), MIP ($r = 0.42$), MEP ($r = 0.5$), PEF ($r = 0.46$) and height ($r = 0.4$) (data not shown). No statistically significant correlation could be found with BMI, Tiffeneau index, FEV1 (L), FEV1 %predicted and FVC %predicted. A stepwise multiple regression was performed on the whole population (n= 40) to study independent predictors of PIF device. It was found that spirometric PIF (partial R^2: 0.25 , $p = 0.0008$) and age (partial R^2: 0.12, $p= 0.014$) independently contributed to explain the variance of PIF device (R^2: 0.37, $p<0.001$). The other variables could not be retained. Stepwise multiple regression for the peak inspiratory flow over the Aeroliser, Diskus and Turbuhaler, could only withhold PIF measured by spirometry as independent predictor ($R^2 = 0.45$ for Aeroliser, $p < 0.001$), ($R^2 = 0.42$ for Diskus, $p < 0.0001$) ($R^2 = 0.39$ for Turbuhaler, $p < 0.001$) (Figure 1).

The In-Check device was preset at resistances corresponding to the airflow resistances of the Aeroliser, Diskus and Turbuhaler. As expected, in COPD patients as well as in the elderly control population, the peak inspiratory flow rates measured by the In-check method were significantly lower with increasing resistances (one-way ANOVA and Bonferonni multiple comparison test, $p < 0.01$)(data not shown). When comparing COPD patients with elderly controls, no statistically significant difference could be observed (two-way ANOVA, $p = 0.09$) on the PIFs between both groups at any given resistance (Figure 2).

PIFs measured by the In-Check method were subsequently divided in 4 different categories: Flows > 60 L/min, flows between 60-45 L/min and 45-30 L/min, and flows < 30 L/min. An arbitrary cut-off was made at 45 L/min in order to distinguish therapeutic flows from sub-therapeutic levels. Therapeutic flows > 45 L/min were obtained in 87.5% (n=35), 80% (n=32) and only 70% (n=28) of cases, respectively for the Aeroliser, Diskus and Turbuhaler. When comparing the flow rates to the previously described minimal flow rate of 30 L/min, 12.5 % (n=5) of the Turbuhaler users was unable to generate the minimal required flow, whereas all patients (n= 40) could attaint this minimal flow when using the Aeroliser or Diskus. A statistically significant difference between COPD patients and elderly controls could not be observed on any of the different categories (Fisher-exact Test, $p > 0.05$).

Discussion

This study examines the peak inspiratory flow that can be generated over different DPIs in an elderly patient population by using the In-check method. We demonstrated that the peak inspiratory flow over a DPI positively correlated with the spirometric PIF, forced vital capacity and maximal inspiratory pressure, whilst a negative but significant correlation could be observed with age. Stepwise multiple regression analysis could only retain spirometric PIF as independent predictor for explaining the variance of PIF across the device at any given resistance. The presence and severity of COPD did never contribute to our model and when comparing elderly COPD patients with matched healthy controls, no difference could be observed in their ability to achieve acceptable flows over the different DPIs tested. Nevertheless, an important part of our patients were not able to reach the PIF that is recommended for an optimal therapeutic effect.

The PIF over a DPI depends on the maximal inspiratory pressure a patient can generate, but also on the resistance attributable to the device and to the patients airways [8]. Our data are consistent with previous reports in asthmatics and COPD patients [5,33,34]. In these publications it was demonstrated that lung function variables predictive for PIF across a DPI were MIP, spirometric PIF and inspiratory capacity, whereas FEV1, as expression of the severity of illness, did not correlate with the maximal inspiratory flow rate over a device. We found similar correlations but could also describe a negative correlation between PIF device and age, which could be expected given the age dependency of PIF in prediction equations. It is therefore very likely that in an elderly population the optimal use of DPIs decreases with age for reasons of reduced inspiratory muscle force, lower spirometric PIF [17] and the fact that with age the correct use of a DPI becomes more difficult [15,16].

Our data could not demonstrate a significant difference between the elderly COPD population and the healthy control group when looking at inspiratory flows across the different devices. Because COPD is above all an expiratory disease which does not directly affect inspiratory flow rates, this finding is not surprising and has already been reported by others [5,34]. In a younger COPD population (mean age: 56) it has been demonstrated that all patients were able to generate PIFs above 50 L/min against several resistances [34]. The authors consequently concluded that each COPD patient could benefit from all the different types of DPIs available.

In our elderly population however, flows below 45 L/min were present in 12.5% of cases (n=5) for the Aeroliser, in 20% of cases (n= 8) for the Diskus and even in 30% of cases (n=12) for the Turbuhaler. This is consistent with the findings of Nsour and collegues who descibed in 31% of COPD patients (n=23/74, mean age: 79) PIFs below 40 L/min when using the Turbuhaler [16]. The fact that Derwa and collegues found subtherapeutic flows below 40 L/min over the Turbohaler in only 17 % of their COPD patients (n=17/100) might be explained by the lower mean age (69) of their population. As in our hands younger patients (n = 15, mean age: 36 years) were all able to achieve PIFs above 60 L/min when using the same device and protocol (data not shown), we believe that age, much more than COPD severity, should be taken into account when prescribing DPI's for stable COPD in an elderly population.

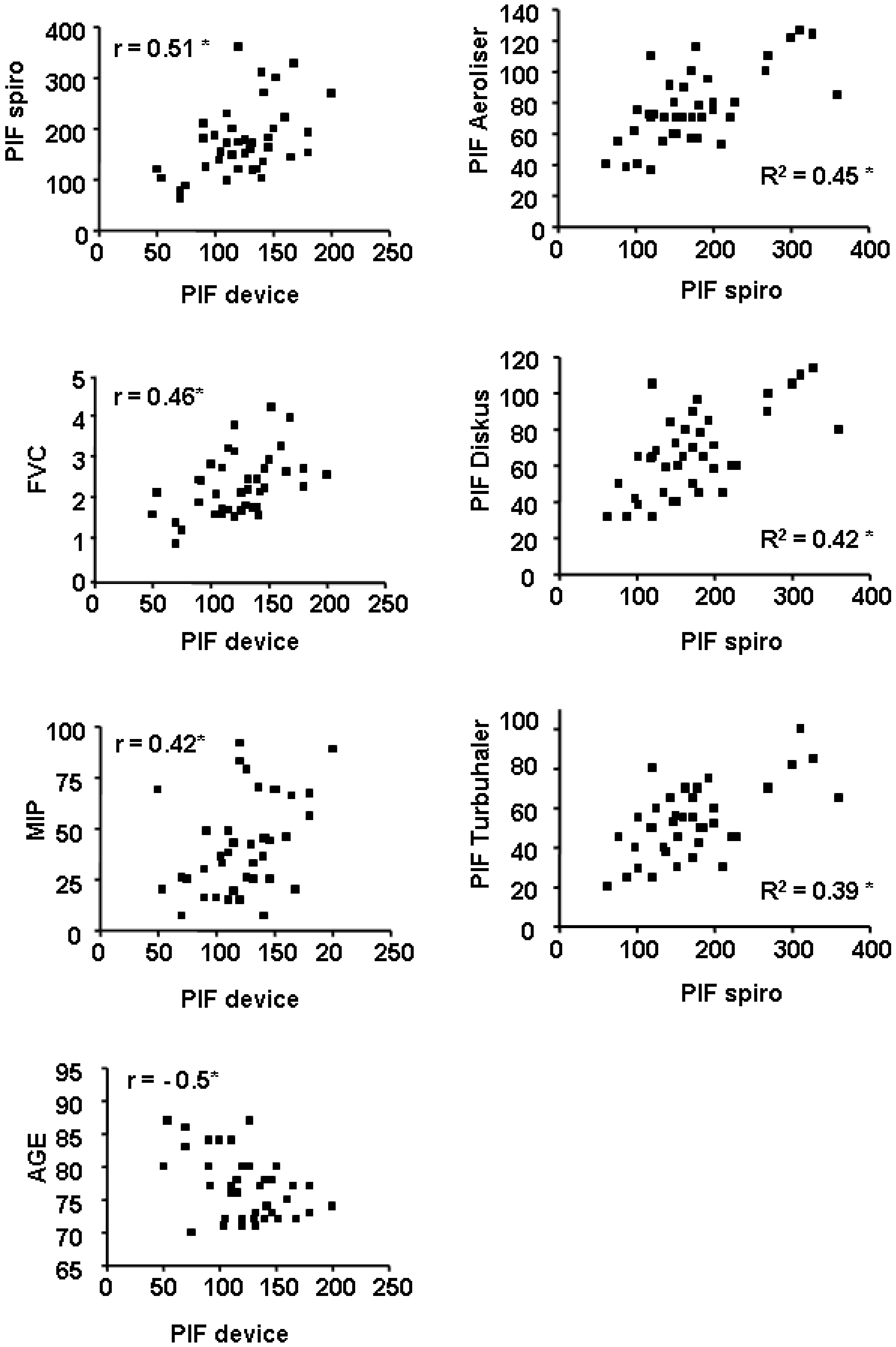
Most authors agree on the fact that in case of reduced inspiratory flow, a low-resistance DPI that is relatively insensitive to changes in airflow will be more beneficial. Manufacturers should therefore be encouraged to label their product with its specific resistance and the dose emitted at different flow rates [14]. Our data demonstrate that 30% of the elderly population were not able to reach the arbitrary cut-off flow of 45 L/min when using a Turbuhaler whilst only 20% and 12.5% of the population had similar problems with the Diskus and Aeroliser, respectively. Turbuhaler and Aeroliser are less effective at a PIF below 60 L/min whereas the Diskus seems to have an equal effect at a PIF between 30 and 60 L/min [6,22-30]. This could mean that in contrast to the Diskus, the number of patients with sub-therapeutic flows over the Aeroliser or Turbuhaler is even underestimated. Whether this sub-optimal flow also results in a different clinical outcome in terms of symptom relief, reduction of exacerbations and lower mortality, is currently not known. This should be further investigated in future studies.

In conclusion, this study demonstrates that in elderly patients the ability to generate sufficient inspiratory flow across a DPI is compromised, irrespective of the presence of COPD. This is an important finding as elderly people are generally encouraged to use a DPI in stead of MDIs because of its easier application. Ideally, the choice for the most appropriate DPI in elderly patients should therefore depend on the objective measurement of PIF against a certain resistance. Alternatively, the direct choice for a low resistance DPI which is relative insensitive to changes in PIF at lower flow levels, might be beneficial in situations like exacerbations characterised by a further reduction of inspiratory flow [12,21,35].

	Elderly COPD (n = 26) Mean ± SD	Elderly controls (n = 14) Mean ± SD	P value
Age (year)	76.0 ± 4.5	79.0 ± 5.6	0.07
BMI (kg/m^2)	25.6 ± 4.0	24.4 ± 2.2	0.3
Length (cm)	167 ± 0.77	165 ± 0.07	0.36
FVC (L)	2.23 ± 0.76	2.61 ± 0.68	0.13
FVC (%pred)	67.6 ± 17	92.6 ± 11	0.001*
FEV1 (L)	1.23 ± 0.59	1.98 ± 0.52	0.003*
FEV1 (%pred)	48.9 ± 20	90.9 ± 11	0.001*
PIF (L/min)	169 ± 66	179 ± 65	0.68
PEF (L/min)	199 ± 99	270 ± 89	0.03*
MIP (cm H_2O)	41.1 ± 22	42.3 ± 26	0.87
MEP (cm H_2O)	77.8 ± 37	67.7 ± 41	0.43

Table 1 : Baseline characteristics of COPD patients and matched elderly controls. Statistically significant differences are indicated by *.

Legends to the figures



r = 0.51 *
PIF spiro
0
100
200
300
400
0
50
100
150
200
250
PIF device
140
120
100
80
60
40
20
0
PIF Aeroliser
R² = 0.45 *
0
100
200
300
400
PIF spiro
r = 0.46*
FVC
5
4
3
2
1
0
0
50
100
150
200
250
PIF device
120
100
80
60
40
20
0
PIF Diskus
R² = 0.42 *
0
100
200
300
400
PIF spiro
r = 0.42*
MIP
100
75
50
25
0
0
50
100
150
20
250
PIF device
100
80
60
40
20
0
PIF Turbuhaler
R² = 0.39 *
0
100
200
300
400
PIF spiro
r = - 0.5*
AGE
95
90
85
80
75
70
65
0
50
100
150
200
250
PIF device

Figure 1 : Plots on left demonstrate statistically significant and clinically relevant correlations of PIF device (L/min) with PIF spirometry (L/min), FVC (% predicted), MIP (cmH_2O) and age (years) in the whole study group (n= 40). Plots on the right represent the correlation of PIF measured by the In-check method with spirometric PIF (L/min) in the whole study population (n = 40) at increasing resistances of Aeroliser, Diskus and Turbuhaler, respectively. (r = Pearson correlation coefficient, R^2 = the fraction of variance explained by regression model)

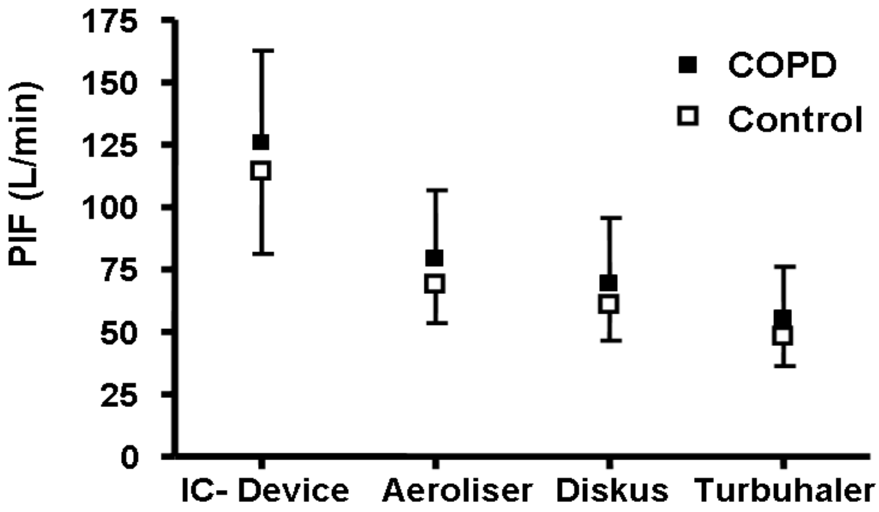


Figure 2 : Mean peak inspiratory flow rates (L/min) and SD as assessed by the In-check Dial method in elderly COPD patients (■, n= 26) and healthy controls (□, n = 14). PIFs over the In-check device (IC-device) are compared with PIFs over increasing additional resistances that correspond to the resistance of the Aeroliser, Diskus and Turbuhaler. In controls or COPD patients the resistance of the device determines PIF across the device (p = 0.01) but presence or absence of COPD is not related (p>0.05).

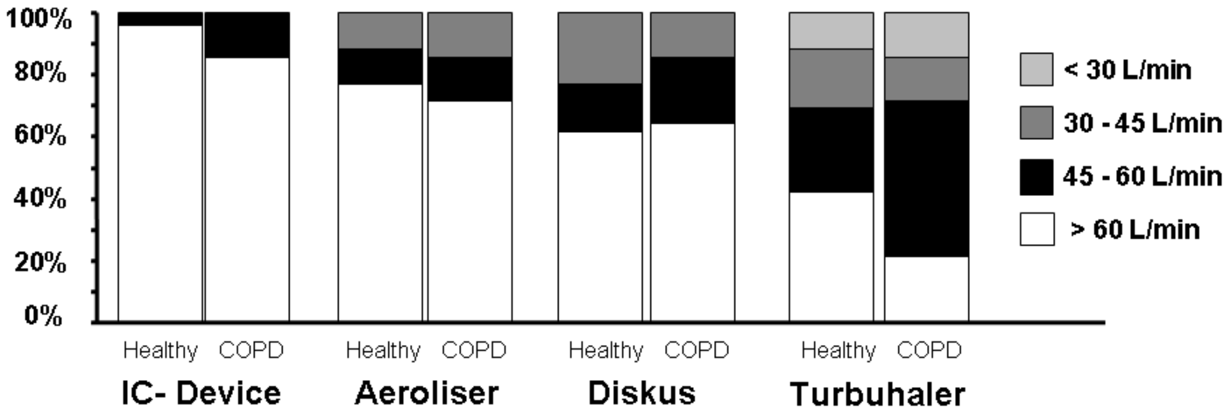


Figure 3 : Bar plot comparing the percentages of patients that achieve PIFs within a certain flow range at different resistances as simulated by the In-Check dial method. COPD patients (n = 26) are compared with matched healthy controls (n = 14).

References

1. Jones V, Fernandez C, Diggory P**.** A comparison of large volume spacer, breath-activated and dry powder inhalers in older people. *Age Ageing* 1999; 28: 481-484.

2. Roche N, Chinet T, Huchon G**.** Ambulatory inhalation therapy in obstructive lung diseases. *Respiration* 1997; 64: 121-130.

3. Sumby B, Slater A, Atkins PJ, Prime D**.** Review of dry powder inhalers. *Adv Drug Deliv Rev* 1997; 26: 51-58.

4. Broeders ME, Molema J, Vermue NA, Folgering HT**.** Peak inspiratory flow rate and slope of the inhalation profiles in dry powder inhalers. *Eur Respir J* 2001; 18: 780-783.

5. Broeders ME, Molema J, Hop WC, Folgering HT**.** Inhalation profiles in asthmatics and COPD patients: reproducibility and effect of instruction. *J Aerosol Med* 2003; 16: 131-141.

6. Broeders ME, Molema J, Vermue NA, Folgering HT**.** In Check Dial: accuracy for Diskus and Turbuhaler. *Int J Pharm* 2003; 252: 275-280.

7. Bronsky EA, Grossman J, Henis MJ, Gallo PP, Yegen U, Della CG, Kottakis J, Mehra S**.** Inspiratory flow rates and volumes with the Aerolizer dry powder inhaler in asthmatic children and adults. *Curr Med Res Opin* 2004; 20: 131-137.

8. Clark AR and Hollingworth AM**.** The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers--implications for in vitro testing. *J Aerosol Med* 1993; 6: 99-110.

9. Amirav I, Newhouse MT, Mansour Y**.** Measurement of peak inspiratory flow with in-check dial device to simulate low-resistance (Diskus) and high-resistance (Turbohaler) dry powder inhalers in children with asthma. *Pediatr Pulmonol* 2005; 39: 447-451.

10. Adachi YS, Adachi Y, Itazawa T, Yamamoto J, Murakami G, Miyawaki T**.** Ability of preschool children to use dry powder inhalers as evaluated by In-Check Meter. *Pediatr Int* 2006; 48: 62-65.

11. Broeders ME, Molema J, Hop WC, Vermue NA, Folgering HT**.** The course of inhalation profiles during an exacerbation of obstructive lung disease. *Respir Med* 2004; 98: 1173-1179.

12. Richter K**.** Successful use of DPI systems in asthmatic patients--key parameters. *Respir Med* 2004; 98 Suppl B: S22-S27.

13. 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.

14. Chrystyn H**.** Is inhalation rate important for a dry powder inhaler? Using the In-Check Dial to identify these rates. *Respir Med* 2003; 97: 181-187.

15. Diggory P, Fernandez C, Humphrey A, Jones V, Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *BMJ* 2001; 322: 577-579.

16. 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.

17. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999; 13: 197-205.

18. Jarvis S, Ind PW, Shiner RJ. Inhaled therapy in elderly COPD patients; time for re-evaluation? *Age Ageing* 2007.

19. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16: 5-40.

20. Black LF and Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; 99: 696-702.

21. van der PJ. 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.

22. Meakin BJ, Ganderton D, Panza I, Ventura P. The effect of flow rate on drug delivery from the Pulvinal, a high-resistance dry powder inhaler. *J Aerosol Med* 1998; 11: 143-152.

23. Prime D, Grant AC, Slater AL, Woodhouse RN. A critical comparison of the dose delivery characteristics of four alternative inhalation devices delivering salbutamol: pressurized metered dose inhaler, Diskus inhaler, Diskhaler inhaler, and Turbuhaler inhaler. *J Aerosol Med* 1999; 12: 75-84.

24. Bisgaard H, Klug B, Sumby BS, Burnell PK. Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. *Eur Respir J* 1998; 11: 1111-1115.

25. Chew NY and Chan HK. In vitro aerosol performance and dose uniformity between the Foradile Aerolizer and the Oxis Turbuhaler. *J Aerosol Med* 2001; 14: 495-501.

26. Borgstrom L. Deposition patterns with Turbuhaler. *J Aerosol Med* 1994; 7: S49-S53.

27. 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.

28. Nielsen KG, Auk IL, Bojsen K, Ifversen M, Klug B, Bisgaard H. Clinical effect of Diskus dry-powder inhaler at low and high inspiratory flow-rates in asthmatic children. *Eur Respir J* 1998; 11: 350-354.

29. Tarsin WY, Pearson SB, Assi KH, Chrystyn H**.** Emitted dose estimates from Seretide Diskus and Symbicort Turbuhaler following inhalation by severe asthmatics. *Int J Pharm* 2006; 316: 131-137.

30. Nielsen KG, Skov M, Klug B, Ifversen M, Bisgaard H**.** Flow-dependent effect of formoterol dry-powder inhaled from the Aerolizer. *Eur Respir J* 1997; 10: 2105-2109.

31. 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.

32. Dewar MH, Jamieson A, McLean A, Crompton GK**.** Peak inspiratory flow through Turbuhaler in chronic obstructive airways disease. *Respir Med* 1999; 93: 342-344.

33. Parry-Billings M, Birrell C, Oldham L, O'Callaghan C**.** Inspiratory flow rate through a dry powder inhaler (Clickhaler) in children with asthma. *Pediatr Pulmonol* 2003; 35: 220-226.

34. Sarinas PS, Robinson TE, Clark AR, Canfield J, Jr., Chitkara RK, Fick RB, Jr. Inspiratory flow rate and dynamic lung function in cystic fibrosis and chronic obstructive lung diseases. *Chest* 1998; 114: 988-992.

35. Cegla UH**.** Pressure and inspiratory flow characteristics of dry powder inhalers. *Respir Med* 2004; 98 Suppl A: S22-S28.