

# Inhalation profiles through the Prohaler dry powder inhaler in healthy subjects, and in patients with asthma or chronic obstructive pulmonary disease (COPD)

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## Summary

Inhalation parameters were measured in healthy subjects (n=10) and in asthmatic (n=22) or COPD (n=19) patients through the Prohaler DPI (Valois), before and after training about correct inhaler use. The Prohaler only triggers above a preset inhaled flow rate, and has a relatively high airflow resistance. Mean (SD) peak inhaled flow rates (PIFRs) before training and after training were as follows. Healthy subjects: 29.5 (7.5) L/min vs 36.9 (6.2) L/min; Asthmatics: 26.6 (14.1) L/min vs 33.0 (10.3) L/min; COPD: 23.6 (12.8) L/min vs 32.7 (8.4) L/min. After training, PIFR did not vary significantly between the three subject groups, and was not correlated with forced expiratory volume in one second (FEV<sub>1</sub>). All patients could trigger the device after training, and 37 of 38 patients with quantifiable data could trigger the device and inhale  $\geq 0.75$  L air after triggering. Careful training about correct device use may be the single most important factor determining a patient's ability to use a DPI.

## Introduction

In most dry powder inhalers (DPIs) used by patients with asthma or chronic obstructive pulmonary disease (COPD), the powder is dispersed by the patient's inhalation through the device. The lung dose is likely to depend upon the degree of inspiratory effort. A novel multi-dose breath-actuated dry powder inhaler (Prohaler, Valois) has been developed, containing a series of doses in blisters (Figure 1). Compared to many other DPIs, the Prohaler has a relatively high resistance to airflow, so that maximal inhalation through the device is unlikely to generate a peak inhaled flow rate (PIFR)  $> 50$  L/min. In order to ensure that there is sufficient air flow to disperse the powder efficiently, the device does not trigger unless the inhaled flow rate exceeds a set value (14 L/min in these studies).



**Figure 1.** Prohaler DPI (Valois), showing tubing used to record pressure at mouthpiece.

The objectives of these studies were as follows: (i) to determine how readily patients could trigger the Prohaler, (ii) to measure inhaled flow rate, acceleration and inhaled volume through the Prohaler in healthy subjects, in patients with asthma, and in patients with COPD, and (iii) to assess the effects on these parameters of training about inhaler use.

## Methods

In order to monitor inhalation profiles through the Prohaler, a thin plastic tube (2 mm diameter) was connected to the device mouthpiece (Figure 1), in such a way that the normal functioning of the device was unaffected, and that an adequate seal between the lips and the mouthpiece could be achieved. The plastic tube was connected to a pressure sensor which was connected to a computer, and recorded the differential pressure between the mouth and the atmosphere every 20 msec. Since the inhaled flow rate is proportional to the square root of the differential pressure (1), measurement of pressure allowed peak inhaled flow rate (PIFR), maximal acceleration, and inhaled volume to be calculated.

Inhalation profiles were measured in three groups of subjects, as listed in Table 1. The degree of airflow obstruction was assessed from the forced expiratory volume in one second (FEV<sub>1</sub>), expressed as a percentage of the value predicted on the basis of each subject's sex, age and height. FEV<sub>1</sub> was measured by spirometer. Both patient groups included patients with a wide range of airflow obstructions, ranging from mild to severe. Patients were receiving treatment for their asthma or COPD from a variety of inhaler devices, including pressurized metered dose inhalers, DPIs and nebulisers.

**Table 1.** Subject demographics (M=male, F=female). Mean and range are given for age and FEV<sub>1</sub>.

<u>Group</u>	<u>Number</u>	<u>Age (y)</u>	<u>FEV<sub>1</sub> (% predicted)</u>
Healthy subjects	10 (5M, 5F)	33 (23-39)	98 (81-109)
Asthmatics	22 (10M, 12F)	54 (19-76)	73 (27-102)
COPD	19 (15M, 4F)	69 (51-84)	49 (26-91)

Each subject performed inhalations before and after training about correct inhaler use. Before training, the subject was given a set of device usage instructions, and was allowed to study them unsupervised for 5 minutes. The device usage instructions required the patient to exhale fully away from the device, place the mouthpiece in the mouth making a tight seal with the lips, inhale with a rapid and steady flow until the lungs were full, and then hold the breath for 10 sec. The subject was then asked to inhale through the Prohaler according to the instructions. The inhalation manoeuvre was repeated twice, providing three data sets. The instructions were then carefully explained to the subject by an experienced staff member, and any deviations from correct technique noticed previously were discussed with the subject. Three further inhalations were then performed through the Prohaler, taking into account the training received, and providing three data sets after training. The inhalations giving the best of three PIFRs before training, and the best of three PIFRs after training, were used in the data analysis.

## Results

### *Device triggering*

All the healthy subjects could trigger the Prohaler both before and after training. Before training, 17 of 22 asthmatic patients and 14 of 19 COPD patients triggered the device. All 41 patients could trigger the device after training.

### *Inhaled volumes*

Inhalation data could only be quantified in 38 of 41 patients (one asthmatic patient and one COPD patient had breathing patterns characterised by a series of rapid shallow breaths, and in another asthmatic patient the recording equipment malfunctioned). Inhaled volumes (Table 2) were higher in healthy subjects than in patients ( $P < 0.05$ ), and were higher in males than in females ( $P < 0.05$ ).

**Table 2.** Mean (SD) inhaled volumes (L) before training and after training in three subject groups.

<u>Group</u>	<u>Before training</u>	<u>After training</u>
Healthy subjects (n=10)	2.55 (1.14)	3.23 (1.19)
Asthmatics (n=20)	1.64 (0.88)	1.99 (0.74)
COPD (n=18)	1.48 (1.00)	1.77 (0.60)

After training, 37 of 38 patients with quantifiable data could both trigger the device and follow triggering with inhalation of  $\geq 0.75$  L air (mean inhaled volumes of 1.99 L in asthmatic patients, and 1.77 L in COPD patients).

#### Peak inhaled flow rates

The PIFRs before and after training are shown in Table 3.

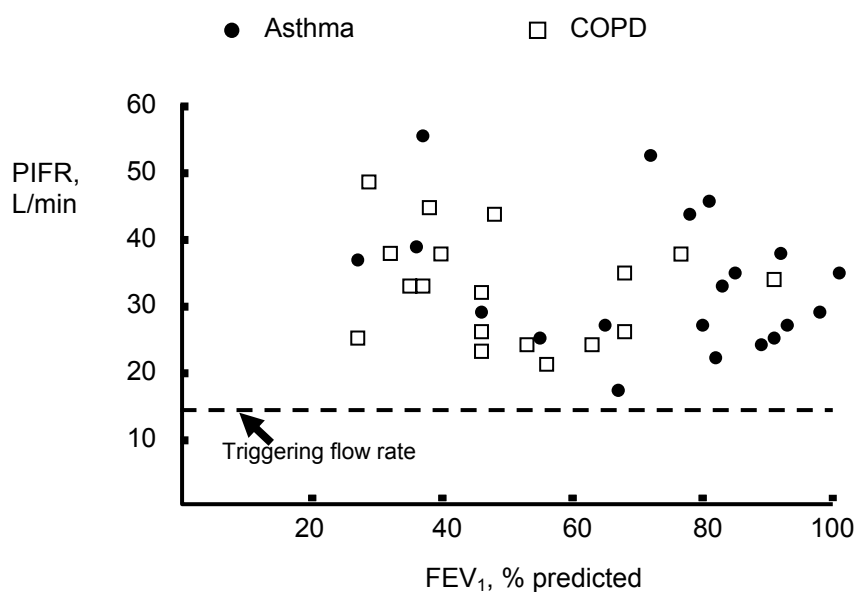
**Table 3.** Mean (SD) PIFRs (L/min) before training and after training in three subject groups.

The asterisk denotes a statistically significant increase in PIFR after training ( $P < 0.05$ ).

Group	Before training	After training
Healthy subjects (n=10)	29.5 (7.5)	36.9 (6.2)*
Asthmatics (n=20)	26.6 (14.1)	33.0 (10.3)
COPD (n=18)	23.6 (12.8)	32.7 (8.4)*

Nine of 10 healthy subjects had PIFRs  $> 20$  L/min before training, and PIFR was 14.9 L/min in the remaining subject. After training, the mean PIFR was increased from 29.5 L/min to 36.9 L/min, and 9 of 10 subjects had a PIFR  $> 30$  L/min.

PIFR in the patient groups was highly variable before training, but after training, there were increases in mean PIFR, and a reduction in its variability. After training, PIFR was not significantly different between healthy subjects, asthmatic patients and COPD patients, and was not correlated with FEV<sub>1</sub> (Figure 2). PIFR did not differ between males and females, but was inversely correlated with age in the COPD patients ( $P < 0.05$ ).



**Figure 2.** PIFR after training as a function of FEV<sub>1</sub> in patients with asthma and COPD.

#### Maximal acceleration

Maximal acceleration was highly variable between individuals (Table 4), and did not vary significantly between the subject groups.

**Table 4.** Mean (SD) maximal acceleration (L/s<sup>2</sup>) before training and after training.

Group	Before training	After training
Healthy subjects (n=10)	2.25 (0.95)	4.00 (2.47)
Asthmatics (n=20)	3.40 (1.84)	2.65 (1.11)
COPD (n=18)	2.81 (2.55)	3.70 (3.87)

In healthy subjects there was a clear increase in maximal acceleration as a result of training. However, the effect of training on maximal acceleration was more mixed in the two patient groups, with a decrease in mean acceleration after training in asthmatics, but an increase in COPD patients.

## Discussion

The inhalation profiles via Prohaler DPI in young healthy volunteers were considered likely to represent optimal device use, against which inhalation profiles in patients with airways obstruction could be compared. Forceful inhalation through DPIs is usually recommended in order to ensure efficient dispersion of powder and a high lung dose (2). A high PIFR through a DPI is generally used as the most practical measure of forceful inhalation, although the numerical value of PIFR will depend on the resistance of the device. For low resistance devices such as Rotahaler and Spinhaler, PIFRs > 100 L/min can be achieved, while for high resistance devices such as Prohaler and Handihaler, PIFR is likely to be < 50 L/min. There is no evidence that low resistance DPIs are inherently superior to high resistance devices, or vice-versa.

In addition to attaining a high PIFR, a patient needs to inhale an adequate volume of air. After training, all but one patient could inhale at least 0.75 L of air following triggering. In order to optimize de-aggregation of particles in the inhaled air stream, the peak inhaled flow should be attained as early as possible in the breath (3), implying the need for a high flow acceleration.

These data suggest that provided they are appropriately trained, virtually any adult patient can trigger the Prohaler, can achieve a satisfactory PIFR through the device, and can follow triggering by inhaling an adequate volume of air. Concerns are sometimes raised that patients with severe airways obstruction might be unable to inhale sufficiently forcefully through DPIs, but PIFRs in patients in this study after training did not differ significantly from those in healthy subjects, and were not correlated with FEV<sub>1</sub>. A review of other data in situations where PIFR might be reduced concluded most patients are able to generate sufficient PIFRs to use a DPI successfully (4). However, in clinical practice, some patients may not inhale forcefully through DPIs, despite being able to do so (5). The importance of educating patients to use correct inhaler technique is recognized as one of the keys to successful pulmonary drug delivery (6). In this study, training increased the mean PIFR, and reduced its variability, as has been observed for other DPIs (7). Careful training about correct device use may be the single most important factor determining a patient's ability to use a DPI.

## References

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