Eur Respir J
1990, 3, 1037–1041

Peak inspiratory flow and inspiratory vital capacity of patients with asthma measured with and without a new dry-powder inhaler device (Turbuhaler®)

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Peak inspiratory flow and inspiratory vital capacity of patients with asthma, measured with and without a new dry-powder inhaler device (Turbuhaler®). T. Engel, J. H. Heinig, F. Madsen, K. Nikander.

ABSTRACT: In 101 asthmatic adults with varying degrees of bronchial obstruction, lung function tests including peak inspiratory flow (PIF), inspiratory vital capacity (IVC), peak expiratory flow (PEF), forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1) measurements were made. Significant correlations between inspiratory and expiratory volumes were found. In most patients, PIF was less reduced than the expiratory parameters of pulmonary function. When inhalation was performed through the new multi-dose, dry-powder inhalation device, Turbuhaler (PIF-TBH), it was significantly lower than PIF measured without Turbuhaler. In previous studies, PIF-TBH of 30 $l \cdot min^{-1}$ or more has proven sufficient to produce a therapeutic dose of terbutaline, and to produce significant bronchodilatation. Of 101 asthmatics in the present study, only four had PIF-TBH of less than 30 $l \cdot min^{-1}$. Although no parameters of spirometry could accurately predict PIF-TBH, there was a tendency for patients with severely impaired ventilatory capacity to produce lower PIF-TBH than patients with normal or near-normal ventilatory capacity. If patients with severely impaired ventilatory capacity are to receive inhalation therapy through Turbuhaler, either PIF or PIF-TBH should be measured, or the effect should be carefully monitored.

Eur Respir J., 1990, 3, 1037–1041.

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Keywords: Asthma; dry-powder inhalers; inspiratory vital capacity; peak expiratory flow; peak inspiratory flow; Turbuhaler.

Received: December 1989; accepted after revision July 24, 1990.

Episodic air flow limitation is a hallmark of bronchial asthma. The aim of pharmacological treatment of bronchial asthma is to reverse the airflow obstruction, and alterations in lung function parameters are, therefore, essential in the evaluation of asthma treatment. Most investigations have focused on the expiratory flow dynamics and the features limiting ventilation. In contrast, little attention has been paid to the features limiting the inspiratory flows in asthmatics, even though these features may be essential for the administration of inhaled drugs.

During the last 20–25 yrs, local inhalation therapy of asthma has been increasingly applied. This is probably due to the introduction of both more potent drugs for local use [1], and simple inhalation devices like spacers and dry-powder inhalers. Dry-powder inhalers may be advantageous compared with metered dose aerosols. They are breath-actuated and do not contain fluorocarbons and lubricants, which may increase the bronchial obstruction [2, 3]. To enable the drug particles to deaggregate, the inhalation flow through the dry-powder inhalers must reach a certain minimum level, which varies for different inhalers and drugs. More attention should, therefore, be devoted to measurements of inspiratory maximal flows and lung volumes, particularly in asthmatic patients.

The aims of the present investigation were: 1) to investigate peak inspiratory flow (PIF) and inspiratory vital capacity (IVC) in asthmatics, and to compare these values with the results of expiratory pulmonary measurements; 2) to study PIF and IVC measured through Turbuhaler; 3) to search for predictors within expiratory spirometry for maximum inspiratory flows through Turbuhaler.

Materials and methods

Patients

During a 4 wk period, all asthmatic patients attending the out-patient allergy clinic were consecutively referred for pulmonary function testing, including inspiratory measurements. The investigations were made regardless of the time interval since the last intake of asthma medication.

After informed consent, 101 patients (38 men, 63 women) with variable chronic obstructive pulmonary disease (COPD) participated in the study (table 1). The patients had varying degrees of airway obstruction with at least 20% variability in forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) during no more than 2 wks within the preceding 6 mths. No patients were excluded on the basis of low (or normal) pulmonary function, and all categories of patients with variable obstructive airways disease were therefore, represented in the material. No patients had any known musculoskeletal diseases, or laryngeal stenosis. The amended Helsinki II declaration was fully observed.

Table 1. – Descriptive data of the 101 patients

	Males (n=38)	Females (n=63)	p
Age yrs	43.5 (14.9–76.3)	40.4 (15.3–78.7)	0.34
Height cm	176.6 (167–190)	166.6 (150–183)	<0.001
Weight kg	76.9 (58–135)	64.9 (40–103)	<0.001
Duration of asthma yrs	17.8 (1–56)	13.3 (1/2–48)	0.11

Mean values and (ranges) are shown.

Measurement of ventilatory capacity

Measurements of the FEV_1, forced vital capacity (FVC) and PEF were performed at least in triplicate on a calibrated dry wedge Vitalograph spirometer (Vitalograph Ltd, Buckingham, UK). All expiratory values were recorded at body temperature, prevailing atmospheric pressure and saturation (BTPS).

Measurement of the PIF was made according to the European guidelines: "The peak inspiratory flow rate (PIF) is the maximal instantaneous flow achieved during a forced inspiratory flow volume manoeuvre" [4]. Measurements of PIF and IVC were made on a daily calibrated hot-wire flow monitor (Monoghan 403®). The equipment was interfaced with a Nicolet 3091 oscilloscope and a Kipp & Zonen X-Y writer. Curves from the X-Y writer were used only as documentation, as all results were obtained directly from the hot-wire device. Initially, triplicate measurements of PIF and IVC were made. Then, triplicate determinations of maximum flow through a Turbuhaler were made by placing the Turbuhaler between the flow monitor and the mouth, using a specially designed Turbuhaler adaptor. All inspiratory values were recorded at ambient temperature and pressure (ATP).

The highest test result was always used in the statistical analysis. No patient underwent more than eight ventilatory capacity tests. The subsequent statistical analysis only included results with a variability of 5% or less between the two highest consecutive measurements. The index of bronchial obstruction was calculated as:

$$\frac{FEV_1 * 100}{IVC} \ (\%)$$

Normal values for FEV_1 and FVC were obtained from a recent Danish investigation [5]. Normal values for PEF were calculated according to the European recommendations [6], and PIF was calculated according to BASS [7] after calculation of body surface area (BSA) [8]. All data are presented in absolute values (*i.e.* non-normalized), unless specifically stated.

Statistics

All results are shown as mean±SD, unless otherwise stated. The statistical analyses used were the Student's t-test, paired or unpaired as appropriate, and the Pearson product-moment correlation analysis. The 95% tolerance limit was calculated expressing the differences between inspiratory and expiratory values of pulmonary function.

Table 2. – Inspiratory and expiratory flow rates in 101 patients with varying degrees of asthma

	Mean	SD	min	max
FEV_1 *l*	2.38	0.90	0.47	4.28
FEV_1 % pred	68.0	26.2	15.2	107.7
PEF *l*·min⁻¹	322	133	33	597
PEF % pred	69.2	26.2	7.5	132.0
FVC *l*	3.29	0.99	0.61	5.33
FVC % pred	76.3	17.2	19.5	116.0
FEV_1/IVC %	70.1	16.9	24.1	98.8
PIF *l*·min⁻¹	261	105	90	577
PIF % pred	98.0	33.8	28.5	189.3
IVC *l*	3.22	0.97	1.16	5.64
PIF-TBH *l*·min⁻¹	59	16	25	93
IVC-TBH *l*	2.65	0.83	1.03	4.93

FEV_1: forced expiratory volume in one second; % pred: percentage predicted; PEF: peak expiratory flow; FVC: forced vital capacity; IVC: inspiratory vital capacity; PIF: peak inspiratory flow; PIF-TBH: PIF through Turbuhaler; IVC-TBH: IVC through Turbuhaler.

Table 3. – Correlation matrix of expiratory and inspiratory measurements of pulmonary function in 101 asthmatics

		PIF	IVC	PIF-TBH
FEV_1	r =	0.54	0.72	0.31
	p =	<0.001	<0.001	0.001
PEF	r =	0.57	0.65	0.27
	p =	<0.001	<0.001	0.003
FVC	r =	0.59	0.82	0.46
	p =	<0.001	<0.001	<0.001
FEV_1/IVC	r =	0.18	0.20	0.04
	p =	0.052	0.029	0.344

For explanation of abbreviations see legend to table 2.

Results

The results of 101 inspiratory and expiratory flow- and volume-measurements are shown in table 2. The degree of bronchial obstruction ranged from none to severe obstruction.

The measurements of expiratory and inspiratory flows and volumes showed significant correlations (table 3). However, PIF could not be accurately predicted by measurement of PEF (fig. 1). PIF was generally lower than PEF. The ratio of peak inspiratory and expiratory flows was above 1 (indicating PIF > PEF) in the patients with the most severe degree of bronchial obstruction (fig. 2).

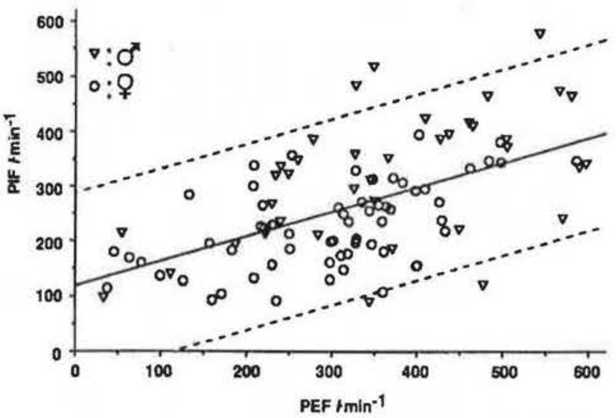

Fig. 1. – Correlation between peak inspiratory flow (PIF) (Y-axis) and peak expiratory flow (PEF) (X-axis) in 101 asthmatic patients. Solid line: line of regression; dotted lines: 95% tolerance limit: SD of the mean difference multiplied by t.

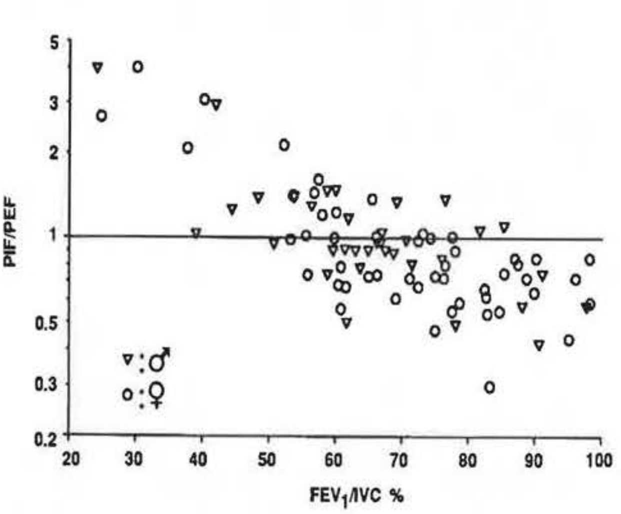

Fig. 2. – Correlation between the ratio of peak inspiratory and expiratory flow: PIF/PEF (Y-axis) and the index of bronchial obstruction (X-axis). Solid line: line of identity (PIF=PEF); FEV_1/IVC: forced expiratory volume in one second as percentage of inspiratory vital capacity.

The IVC/FVC ratio was negatively correlated to the index of bronchial obstruction (FEV_1/IVC) ($p<0.001$, $r=-0.66$). IVC/FVC was above 1 (indicating IVC > FVC) in the patients with the most severe degree of bronchial obstruction.

Although significantly correlated (table 3), measurements through Turbuhaler of PIF (PIF-TBH) and IVC (IVC-TBH) were significantly lower than those without Turbuhaler ($p<0.001$, paired t-test) (table 2). PIF-TBH averaged only 24.5% (±6.9%) of PIF without Turbuhaler. PIF-TBH could not be accurately predicted by measurements of PEF (fig. 3), PIF (fig. 4), FEV_1, or FEV_1/IVC.

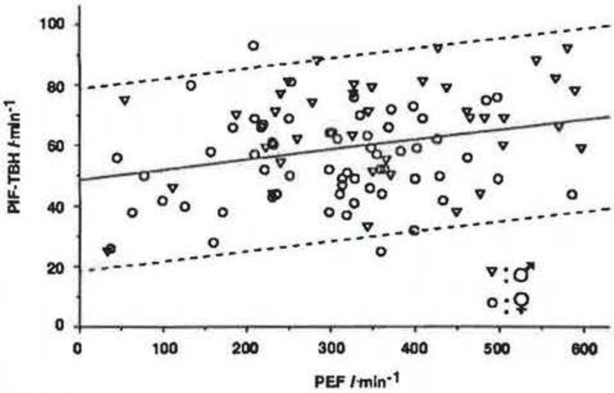

Fig. 3. – Correlation of peak inspiratory flow through Turbuhaler (PIF-TBH), (Y-axis) and peak expiratory flow (PEF) (X-axis) in 101 asthmatic patients. Solid and dotted lines: see legend to figure 1 for explanation.

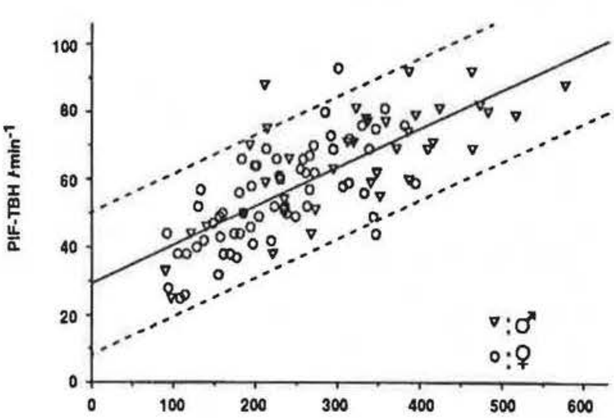

Fig. 4. – Correlation of peak inspiratory flow (PIF) through Turbuhaler, PIF-TBH, (Y-axis) and PIF without Turbuhaler (X-axis) in 101 asthmatic patients. Solid and dotted lines: see legend to figure 1 for explanation.

When inhalation was performed through Turbuhaler, the inhaled volume was less than that without Turbuhaler ($p<0.001$, paired t-test) (table 2). The difference between IVC-TBH and IVC was least pronounced in the patients with the most severe bronchial obstruction.

Of the 101 patients, six were seen in the Allergy Unit during exacerbations of their asthma. They agreed to have their ventilatory capacity measured before and after inhalation of nebulized salbutamol 2.5 mg. Their mean

FEV_1 before inhalation was 2.40±1.0 l, increasing to 2.90±1.46 l 15 min after inhalation. Before the salbutamol inhalation, PIF-TBH averaged 55±17 $l \cdot min^{-1}$. After the salbutamol inhalation, PIF showed a slight but insignificant increase to 59±19 $l \cdot min^{-1}$ ($p=0.4$, paired t-test).

Measurements of the repeatability of PIF-TBH were made in five patients, each undergoing duplicate measurements with an interval of 30 min. The mean difference in PIF-TBH between the measurements was -2.0 $l \cdot min^{-1}$ (95% confidence interval: -6.5–2.5 $l \cdot min^{-1}$).

Discussion

The patients selected for this study represent the average asthma patient attending an out-patient allergy clinic. The patients were consecutively included, and covered a wide range of bronchial obstructions.

Although a significant correlation between PEF and PIF was found, only 32% of the variability in PIF could be explained by PEF ($r^2=0.57^2=0.32$). In the patients with severe bronchial obstruction (very low expiratory ventilatory capacities, PEF and FEV_1), the results of inspiratory ventilatory measurements were generally higher than those of the expiratory ventilatory measurements.

When the effort is increased beyond a certain limit, PEF is mostly dependent on lung dynamics including the degree of bronchial obstruction [9]. In contrast, the maximum inspiratory flow (PIF) is only dependent on the force employed during the manoeuvre and on extrapulmonary limitations such as tracheal stenosis [10]. This impedes normalization of PIF, and only BASS [7] has put forward an equation for calculation of PIF in % predicted. Both KORY *et al.* [11] and FRIDRIKSSON *et al.* [12] have made equations for prediction of PIF, but only for males. The results from our asthmatic patients confirm the difficulties in making such normalization equations. PIF ranged from 29–189% predicted, and showed greater variability than PEF % predicted. In spite of even severe bronchial obstruction, a striking number of our asthmatic patients were able to produce normal or near normal PIF values (above 70% predicted). PIF therefore seems to be less influenced by bronchial obstruction than do the expiratory parameters of ventilatory capacity.

A recent investigation in children with asthma and adolescents with cystic fibrosis found no relationship between inspiratory flows, PIF, maximal inspiratory flow at 75, 50 and 25% FVC, respectively, (MIF_{75}), (MIF_{50}), (MIF_{25}), forced inspiratory volume in one second ($FIV_{.1}$) and airway resistance (Raw) [13]. Furthermore, inhalation of a β-agonist caused significant increase in maximal expiratory flow at 50% FVC (MEF_{50}) and a decrease in Raw, but no change in MIF_{50}. This emphasizes the poor relationship between inspiratory and expiratory parameters of pulmonary function.

No significant difference between IVC and FVC was found. FVC was very low in the severely obstructed patients (minimum value 0.61 l). In agreement with previous findings [14], IVC was higher in these patients (minimum value 1.16 l). The importance of the inspiratory vital capacity during drug inhalation is, however, less known.

The use of dry-powder inhalers such as the new medium-resistance device, Turbuhaler, in the treatment of asthma is increasing. Dry-powder inhalers may be advantageous compared with metered dose aerosols. They are breath-actuated and do not contain fluorocarbons and lubricants, which might cause increased bronchial obstruction [2, 3], and they do not harm the ozone layer.

Turbuhaler is loaded with pure drug without additives such as propellants or vehicles, and is breath-actuated. Generation of inspiratory flows through Turbuhaler of 28 $l \cdot min^{-1}$ or more results in the release of a terbutaline dose of which 25–50% has a mean mass aerodynamic diameter (MMA) <5 μm [15]. Previous studies of mildly disabled asthmatics have shown equal efficacy of terbutaline delivered through metered dose aerosol or through Turbuhaler [16–18], when the inspiratory flow through Turbuhaler is held at about 60 $l \cdot min^{-1}$. A slightly decreased efficacy in the smaller airways has been shown to occur when reducing the peak inspiratory flow through Turbuhaler from 60 to 29 $l \cdot min^{-1}$ [19].

In steroid-dependent asthmatics, equal efficacy on ventilatory capacity was found when budesonide was inhaled through Turbuhaler or conventional metered dose aerosol with spacer attached [20]. However, a significant correlation was found between the peak inspiratory flow generated through Turbuhaler and bronchial responsiveness to inhaled histamine [20], showing decreasing bronchial responsiveness with increased PIF-TBH. This indicates that increased flow through Turbuhaler also results in a better effect when budesonide is inhaled.

Since the present investigation was undertaken before Turbuhaler became commercially available, none of the patients had any previous experience with the use of Turbuhaler. Only 4 of 101 patients had peak inspiratory flows through Turbuhaler of less than 30 $l \cdot min^{-1}$, and none had values below 25 $l \cdot min^{-1}$. Unfortunately, neither PEF, FEV_1, nor FEV_1/IVC were accurate predictors of patients with very low PIF values through Turbuhaler.

In normal children, PIF-TBH varied significantly with age and with PIF [21]. Fifteen of 57 children below 6 yrs of age were unable to generate an inspiratory flow of 28 $l \cdot min^{-1}$. Only one of 208 children ≥6 yrs of age was unable to generate such a flow through Turbuhaler.

The optimal PIF through Turbuhaler may vary for different drugs. In spite of low expiratory flows and volumes, the inspiratory properties may be reduced less. Therefore, even patients with severe bronchial expiratory obstruction may benefit from inhalation therapy. However, either PIF or PIF-TBH should be measured prior to treatment, or the effect should be carefully monitored, if severe bronchial obstruction exists.

Conclusions

Pulmonary function measurements in 101 asthmatic patients showed that:

1. Mean peak inspiratory flow (PIF) was lower than mean peak expiratory flow (PEF). However, in patients with pronounced bronchial obstruction (FEV_1/IVC <50%), PIF was higher than PEF. Inspiratory vital capacity (IVC) was higher than forced expiratory vital capacity (FVC) in patients with pronounced bronchial obstruction.
2. PIF and IVC measured through Turbuhaler, PIF-TBH and IVC-TBH, respectively, were significantly lower than measurements without Turbuhaler. Of 101 asthmatics, only four had PIF values through Turbuhaler below 30 $l \cdot min^{-1}$, which has been shown to give significant bronchodilatation when terbutaline is inhaled through Turbuhaler.
3. No expiratory values could accurately predict the peak inspiratory flow through Turbuhaler.

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Les débits inspiratoires de pointe et la capacité vitale inspiratoire des patients asthmatiques. Mesure avec ou sans l'emploi d'un inhalateur à poudre sèche (Turbuhaler®). T. Engel, J.H. Heinig, F. Madsen, K. Nikander.

RÉSUMÉ: Chez 101 adultes asthmatiques avec différents degrés d'obstruction bronchique, des tests fonctionnels pulmonaires, incluant des mesures inspiratoires (PIF, VIC) et expiratoires (PEF, FVC, VEMS) ont été réalisés. Des corrélations significatives ont été trouvées entre les volumes inspiratoires et expiratiores. Chez la plupart des patients, PIF était moins réduit que les paramètres expiratiores de la fonction pulmonaire. Lorsque l'inhalation est réalisée au travers du nouvel appareil d'inhalation multi-dose à poudre sèche (Turbuhaler), le PIF est significativement plus bas que lorsqu'il est mesuré sans Turbuhaler. Dans les études antérieures, un PIF au travers du Turbuhaler de 30 $l \cdot min^{-1}$ ou davantage s'avère suffisant à produire une dose thérapeutique de terbutaline, et une bronchodilatation significative. Chez les 101 asthmatiques de la présente étude, seuls 4 avaient des valeurs de PIF au travers du Turbuhaler inférieures à 30 $l \cdot min^{-1}$. Quoiqu'aucun paramètre spirométrique ne puisse prédire de façon précise les valeurs de PIF au travers du Turbuhaler, il y avait une tendance, chez les patients dont la capacité ventilatoire était sévèrement atteinte, de produire des valeurs de PIF au travers du Turbuhaler inférieures à celles des patients dont la capacité ventilatoire était normale ou proche de la normale. Si les patients dont la capacité ventilatoire est sévèrement atteinte doivent être soumis à un traitement par inhalation au moyen du Turbuhaler, il faudrait mesurer, soit le PIF soit le PIF-TBH, soit encore mesurer les effets thérapeutiques de façon soigneuse.

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