

Lung characteristics in elderly males and females patients with COPD: differences and optimal use of dry powder inhalers (DPIs)

C. TERZANO, F. ORIOLO

Respiratory Diseases Unit and School of Specialization in Respiratory Diseases Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy

Abstract. – OBJECTIVE: We have measured peak inspiratory flow (PIF), inspiratory capacity (IC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and other functional parameters in COPD patients to investigate which PIF's patients generate with maximal effort, through three different resistances, representing Diskus, Nexthaler and Turbuhaler.

PATIENTS AND METHODS: Forty patients with COPD were enrolled in this study. All patients were examined: pulmonary function tests, including flow/volume spirometry and N₂-wash out, were conducted. MIP and MEP were measured. PIF was measured using the In-check DIAL; patients inhaled through the device set for the optimal Turbuhaler resistance, Nexthaler resistance and Diskus resistance. The relationship between lung function parameters and PIF was studied.

RESULTS: The mean PIF through Nexthaler resistance was significantly higher than the Turbohaler resistance. We have found a mild correlation between PIF and MIP and between PIF, IC and VC.

DISCUSSION: All patients could achieve inspiratory flows > 30 l/min with all inhalers used for the trial. The most interesting result is the mild correlation between MIP and PIF, showing that inspiratory muscle force is probably an important predictor of an adequate inspiratory flow in COPD patients. Many studies confirmed that when using a DPI the inhalation flow is dependent on the resistance of the device and the patient's inspiratory effort.

CONCLUSIONS: Inhalation therapy is the mainstay of treatment of patients with COPD. In the last years, significant developments have been achieved in the field of device formulation, but in daily practice, an appropriate inhaler choice should consider not only device related aspects, but also patient's pulmonary function and in particular patient's respiratory muscle strength.

Key Words:
COPD, PIF, DPIs.

Introduction

COPD is an important cause of morbidity worldwide and it is a chronic disease that continues to increase in prevalence and mortality¹. It is also a risk factor for the presence or development of other chronic illnesses, include cardiovascular diseases², metabolic diseases³, depression, osteoporosis and lung cancer⁴. So optimal treatment of COPD is very important and must also adequately address these other associated processes that can have a considerable impact on the lives of patients.

In the treatment of COPD, inhaled medication plays an important role. The choice of inhaler device should be an integral part of obstructive lung diseases management. For the delivery of a therapeutic agent from an inhalation device to the lungs, a high-quality aerosol with a small particle size (diameter 2-5 µm) must be generated⁵, that enhance the deposition in airways.

Modern local therapy for COPD, that moved the first steps in the development of nebulizers, is now largely based on pressurized metered-dose inhalers (MDIs)⁶. With MDIs the failure to inhale slowly and deeply is often a greater problem than poor coordination⁷; indeed, patients inhale too fast from pMDIs potentially leading to greater impaction of the aerosolized drug in the oropharynx tract and less drug reaching the lungs⁸. Research of alternative to MDIs has accelerated, primarily due to environmental concerns related to the use of chlorofluorocarbons (CFCs): trichlorofluoromethane (P-11), dichlorodifluoromethane (P12) and dichlorotetrafluoroethane (P14), usually mixed, and hydrofluoroalkanes (HFAs) propellants as trifluoromonoethane (P-134) and heptafluoropropane (P-227) have been developed, with different features from CFCs and limited effects on ozone depletion⁹.

The most attractive solution to this problem is represented by the development of dry pow-

Table I. Pressure drop across the device¹⁵.

Low resistance DPIs <5 Mbar 1/2 L/min ⁻¹
Medium resistance DPIs 5-10 Mbar 1/2 L/min ⁻¹
High resistance DPIs >10 Mbar 1/2 L/min ⁻¹

der inhalers (DPIs), that, even if widely variable in design, represent a substantial improvement in the inhalation therapy, in particular they eliminate the use of propellants, simplify the inhalation technique, reduce the patient's cooperation and improve the patient's compliance to treatment¹⁰⁻¹². For a DPI the inhalation has to be deep and forceful to disperse the medication adequately¹³. An inspiratory flow of 30-60 l/min, depending upon the type of inhaler, is necessary to guarantee an optimal lung deposition of the medication¹⁴. All DPIs should be used with a deep inspiration; this type of inhalation maneuvers with a fast initial acceleration rate is necessary so that the resultant turbulent force which occurs inside the inhaler, can break up the formulation of the dose into particles that are most likely to be deposited into the lungs as they join the inspired airstream. The higher the internal force that is generated, the better is the quality of the emitted dose with respect to lung deposition.

All DPIs can be differentiated according to their intrinsic resistive regimen. The performance of each DPI can be affected by only two main driving forces: the inspiratory flow generated by the patient and the turbulence produced inside the device, which depends on its technical characteristics¹⁵. In particular, the inspiratory airflow generated by the patient represents the only active force able to produce the micro-dispersion of the powdered drug to inhale; the extent of the patient's inspiratory airflow depends on the patient's airway and lung conditions. So in order to overcome the

intrinsic resistance of DPIs, the patient has to generate a certain inspiratory flow; these flow rates are depending on the kind of DPI. In fact with the same amount of respiratory work, it was produced a lower flow through a device with high intrinsic resistance compared to one with low resistance.

DPIs can be differentiated according to their intrinsic resistive regimen, such as a constant which depends on the original constructive design of each device, and which is evaluated by measuring the extent of pressure drop across the device itself (Table I).

A technical review on DPIs currently available on the market has been recently carried out to compare in standard conditions their intrinsic characteristics in terms of inspiratory device resistance, of inspiratory flow rate and corresponding pressure drop and of their performance variability¹⁶. The low-resistance DPIs confirmed those requiring the highest inspiratory flow rates for consenting an effective actuation and those characterized by the highest variability in the delivery of respirable fraction of the drug. DPIs, which are characterized by medium intrinsic resistance consent a better performance from this point of view, in fact, they confirmed to require a much lower inspiratory flow rate for an effective actuation. High resistance DPIs, even if allowing a lower inspiratory flow rate, proved to affect particle generation and dispersion of powdered drug (Table II).

In this study we have measured peak inspiratory flow (PIF), inspiratory capacity (IC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and other functional parameters (VC, FVC, FEV₁, PEF, TLC, RV) of patients with COPD in order to investigate which PIF's patients generate with maximal effort, through three different resistances, representing Diskus, Nexthaler and Turbuhaler. Also we would investigate a possible correlation between PIF

Table II. Differences in intrinsic resistance and inspiratory flow rate through the device of some of most commonly used DPIs¹⁶.

	Inspiratory DPI resistance (kPa 0.5 L/min)	Inspiratory flow rate (L/min)
Breezhaler®	0.017	111
Aerolizer®	0-019	102
Ellipta®	0.027	74
Novolizer®	0.027	72
Accuhaler/Diskus®	0.027	72
Genuair®	0.031	64
Nexthaler®	0.036	54
Turbohaler®	0.039	54
Handihaler®	0.058	37

Table III. Patient anthropometric measurements.

Patients	
Number	40 (25 males, 15 females)
Mean age	65 years $\pm$ 6
Body weight	78 $\pm$ 12
Body height	166 $\pm$ 8

and other lung function parameters (particularly MIP). It is well known that a reduction of MIP and MEP can be observed in patients with COPD. The measurement of the maximum static mouth pressures made against an occluded airway (maximal expiratory pressure and maximal expiratory and maximal inspiratory pressure) is the most widely used and is a simple way to gauge respiratory muscle strength and to quantify its severity^{17,18,19}. When we analyze maximal respiratory pressure, we should consider both the difficulty that some subjects have in performing a maximal effort and the normal biological variability of respiratory muscle strength. In an elderly population the optimal use of DPIs decreases with age for reasons of reduced inspiratory muscle force, lower spirometric PIF²⁰ and the correct use of a DPI becomes more difficult^{21,22}.

MIP is the maximum negative pressure that can be generated from one inspiratory effort starting from functional residual capacity (FRC) or residual volume (RV). MEP measures the maximum positive pressure that can be generated from one expiratory effort starting from total lung capacity (TLC) or FRC. MIP and MEP was well studied in patients with COPD by Terzano et al^{23,24}.

Patients and Methods

Forty patients with COPD were enrolled in this study. All patients were in a clinically stable condition and their characteristics were showed in Table III.

Informed consent was obtained for the study that was performed in accordance with the ethical standards of the Declaration of Helsinki. At the moment of the enrollment all the patients were examined: anthropometric measurements (age, height and weight) were taken and pulmonary function tests, including flow/volume spirometry and N₂-wash out, were conducted, using a Cosmed Quark spirometer (PFT4 SUITE, COSMED, Pavona, Rome, Italy). MIP and MEP were measured

using a portable mouth pressure meter (Spirovis, COSMED, Pavona, Rome, Italy): MIP was obtained at the level of RV and MEP was measured at the level of the TLC. PIF was measured using the In-check DIAL; patients inhaled through the device set for the optimal Turbuhaler resistance (60 l/min), Nexthaler resistance (50 l/min) and Diskus resistance (40 l/min). To stimulate the patients all manoeuvres were executed under the supervision of a well-trained lung function assistant and the highest values of three attempts were recorded for all parameters.

The relationship between lung function parameters and PIF was studied by mean of correlation and multiple logistic regression analysis. The difference in continuous variables between resistances, were studied by the t-test with 95% confidence intervals.

Results

Forty patients (25 males and 15 females) with a mean age of 65 years were included in the study. Lung function characteristics are showed in Table IV.

The mean PIF through Nexthaler resistance was 108 l/min (SD 7.9), which was significantly higher than the 102 l/min (SD 7.2) through the Turbuhaler ($p = 0.005$). No significant differences were found between the mean PIF through Nexthaler resistance and the mean PIF through Diskus resistance (mean 104 l/min, SD 8.8, $p = 0.07$) and between the mean PIF through Diskus resistance and Turbuhaler ($p = 0.4$) (Figures 1 and 2).

We have found a mild correlation between PIF and MIP and between PIF, IC and VC. No correlation was found between PIF and other lung function parameters we are measured. The correlation coefficients are showed in Table V.

For the 25 males, the mean PIF through the Nexthaler resistance was 115 l/min, through the Turbuhaler was 103 l/min, through Diskus was 104 l/min, with a significant difference also between Nexthaler and Diskus ($p = 0.03$) (Figures 3 and 4).

For the 15 females the mean PIF through the Nexthaler resistance was 107 l/min, through the Turbuhaler was 103 l/min, through Diskus was 102 l/min, with a significant difference also between Nexthaler and Turbuhaler ($p = 0.02$) (Figures 5 and 6).

The difference between males and females was significant only for the mean PIF through Nexthaler resistance ($p = 0.01$).

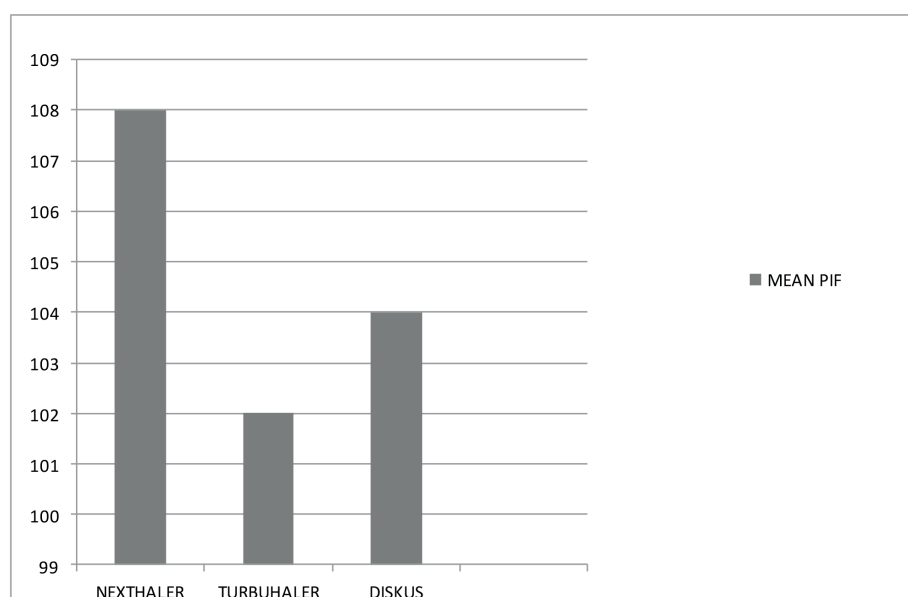


Figure 1. Mean PIF (l/min) for patients inhaling through the In-Check DIAL calibrated for the optimal Nexthaler, Turbuhaler and Diskus resistance.

Table IV. Lung function measurements.

Lung function measurements	Patients (n° 40)	Males (n°25)	Females (n°15)
FVC%	85.6 +/- 13.6	84.5 +/-12.7	83.5 +/-11.7
FEV1%	69.6 +/- 6	68.9 +/- 5.6	67.9 +/- 5.6
PEF%	74.05 +/- 11.5	71.5 +/- 6.4	69.5 +/- 6.4
MMEF25-75%	41 +/- 7.3	39.3 +/- 6.9	37.3 +/- 6.9
IC%	88.4 +/- 10.2	80.5 +/- 12.3	78.5 +/- 11.3
VC%	111.6 +/-13.5	99.5 +/- 13.7	95.5 +/- 10.7
RV%	129.4 +/- 16.7	125.7 +/-14.4	121.8 +/-12.3
TLC%	108.9 +/-9.9	107.1 +/- 15.8	101.1 +/- 12.5
MIP (cm H ₂ O)	80 +/- 34	80 +/- 10.5	75 +/- 9.1
MEP (cmH ₂ O)	90 +/-32	89+/-33	87+/-31

Table V. Correlation coefficients.

	MIP	IC	VC
PIF through NEXTHALER	0.417	0.516	0.511
PIF through TURBUHALER	0.421	0.418	0.492
PIF through DISKUS	0.419	0.415	0.416

Discussion

It is well known that the critical factors driving the therapeutic effectiveness of a respiratory drug assumed through a DPI are represented by the constructive constants of the device and by the generation of an inhalation airflow rate sufficient to trigger the dose and disaggregate the drug. So together with the formulate aspects, the

design of a device, with the potential to generate an airflow capable of aerosolizing the dose in a respirable high fraction, representing a crucial point for the therapeutical success of a DPI.

In general, comfortable devices in terms of use, have to be considered only those who required a limited inhalator effort from the patient in order to reach efficient flow rate and it has been determined that this effort not exceeds 50% of maximal

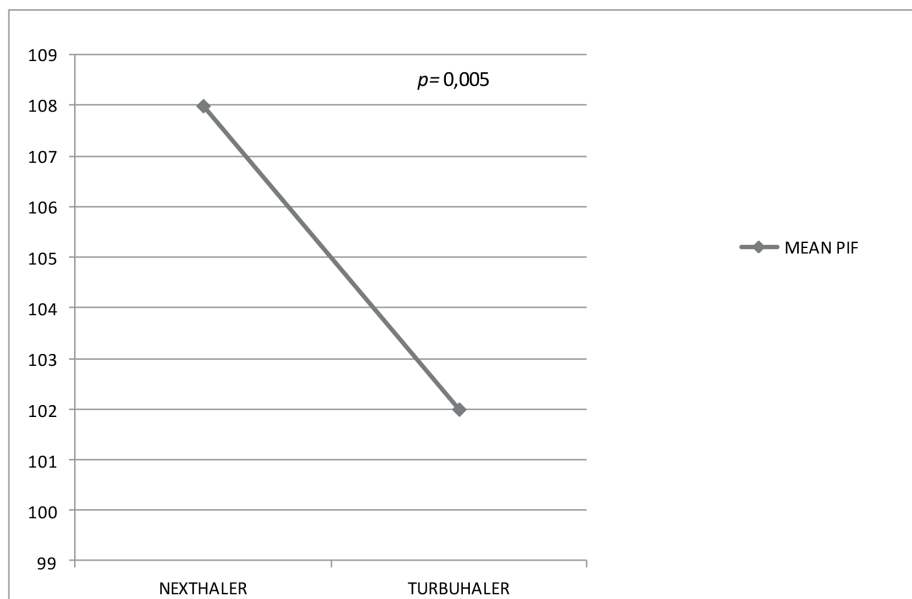


Figure 2. Difference between means PIF (l/min) through Nexthaler resistance and Turbuhaler resistance.

effort²⁵. The marketed DPIs show different resistance to the inspiratory act: high resistance can generate high turbulence, with more difficult breath through the device.

There are many devices available and the choice of the most appropriate for each patient is very difficult for the prescriber. The In-Check DIAL has been introduced in order to assess the

inspiratory effort of patients using a selection of DPIs^{26,27}.

In this study, all patients could achieve inspiratory flows > 30 l/min with all inhalers we have used for the trial (Nexthaler, Turbuhaler and Diskus). The most interesting result, in our study, is the mild correlation we have found between MIP and PIF, showing that inspiratory muscle force is

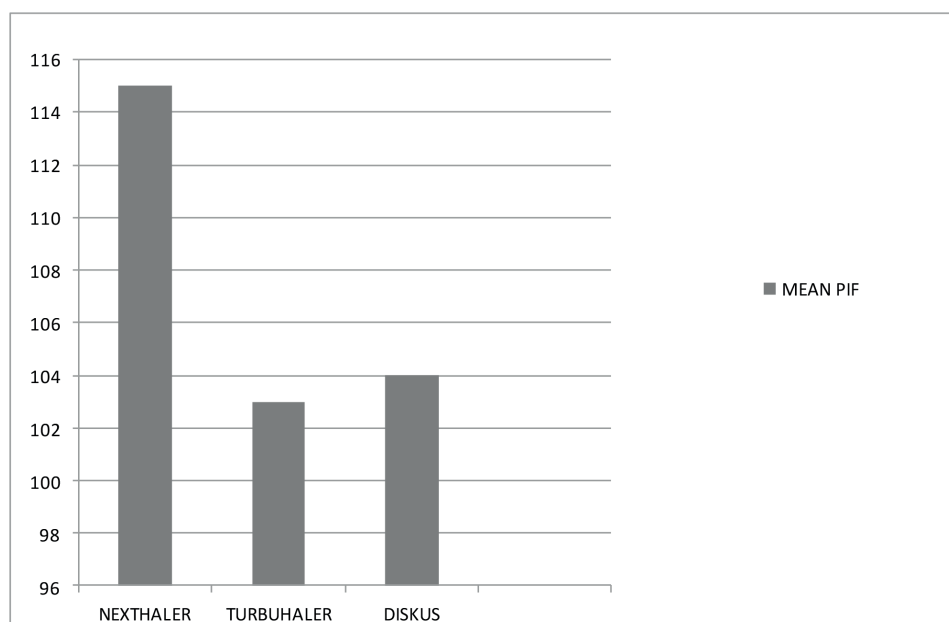


Figure 3. Mean PIF (l/min) for male patients (n=25) inhaling through the In-Check DIAL calibrated for the optimal Nexthaler, Turbuhaler and Diskus resistance.

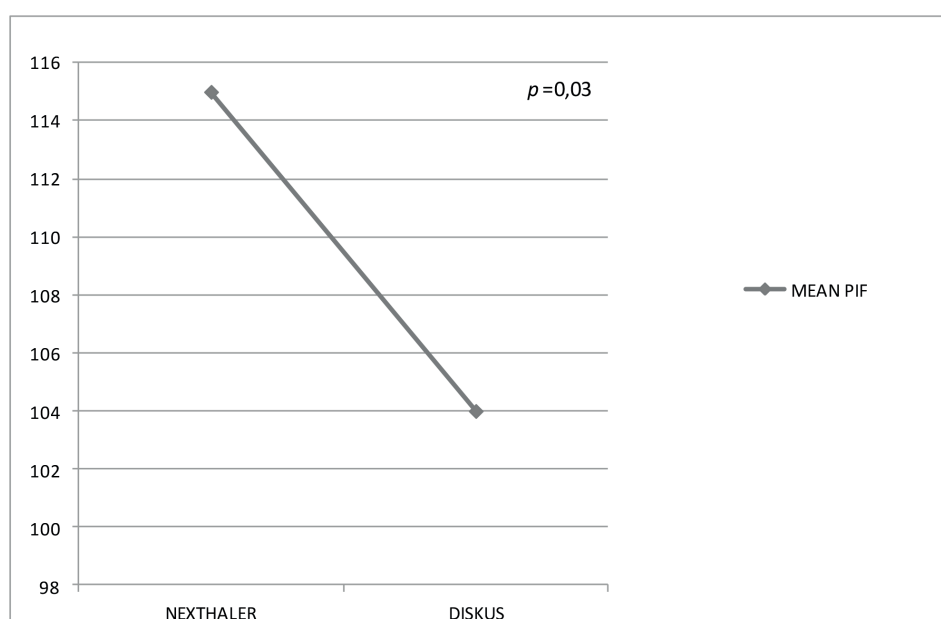


Figure 4. Difference between means PIF (l/min) through Nexthaler resistance and Diskus resistance in male patients.

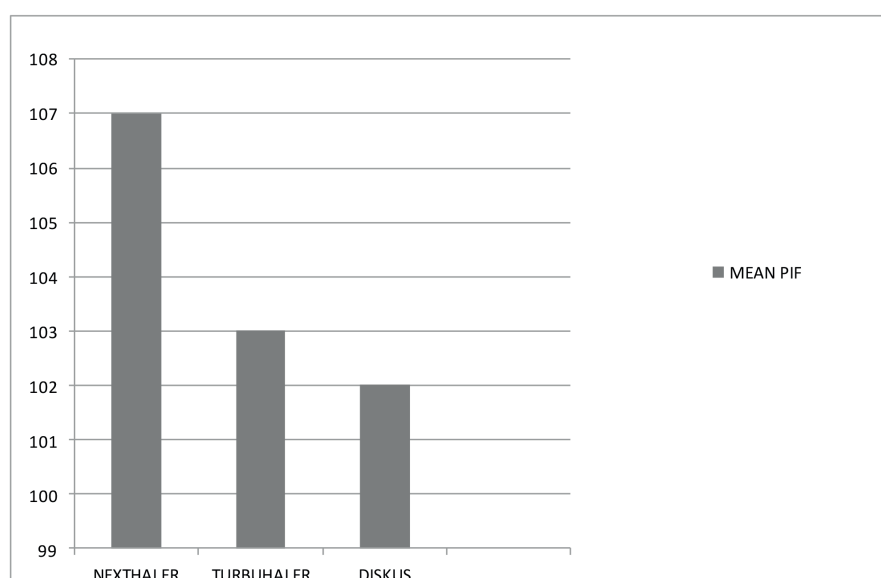


Figure 5. Mean PIF (l/min) for female patients (n=15) inhaling through the In-Check DIAL calibrated for the optimal Nexthaler, Turbuhaler and Diskus resistance.

probably an important predictor of an adequate inspiratory flow in COPD patients²⁸⁻³⁰. It is well known that a reduction of MIP and MEP can be observed in patients with COPD, for many reasons, such as malnutrition, muscular atrophy, steroid induced myopathy, pulmonary hyperinflation with increased residual volume and reduced blood flow to the respiratory muscles^{23,31-33}.

In our patients, we have found a significant difference between PIF generated through Nexthaler resistance and the PIF through Turbuhaler resistance, with a mean value higher for the Nexthaler, without significant differences between Nexthaler and Diskus and between Turbuhaler and Diskus, if we consider the totality of the patients we have studied.

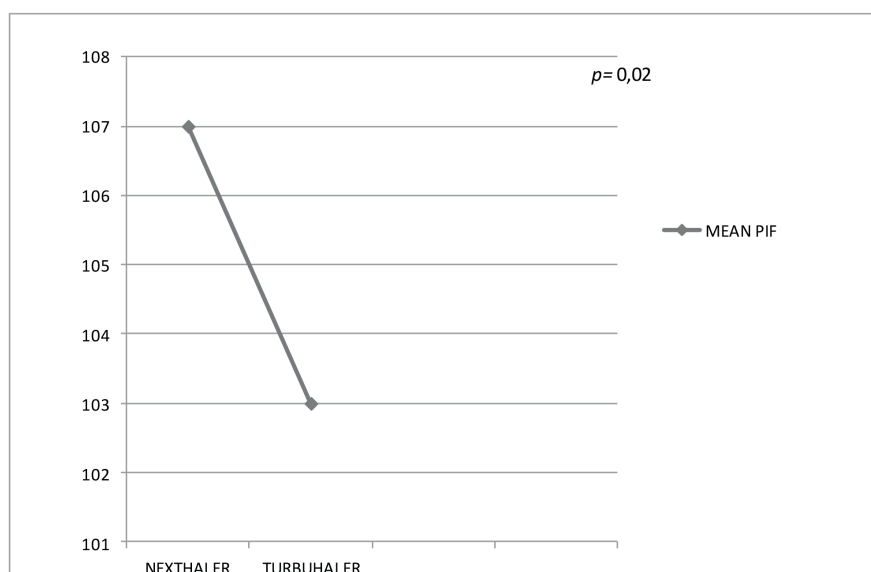


Figure 6. Difference between means PIF (l/min) through Nexthaler resistance and Turbuhaler resistance in female patients.

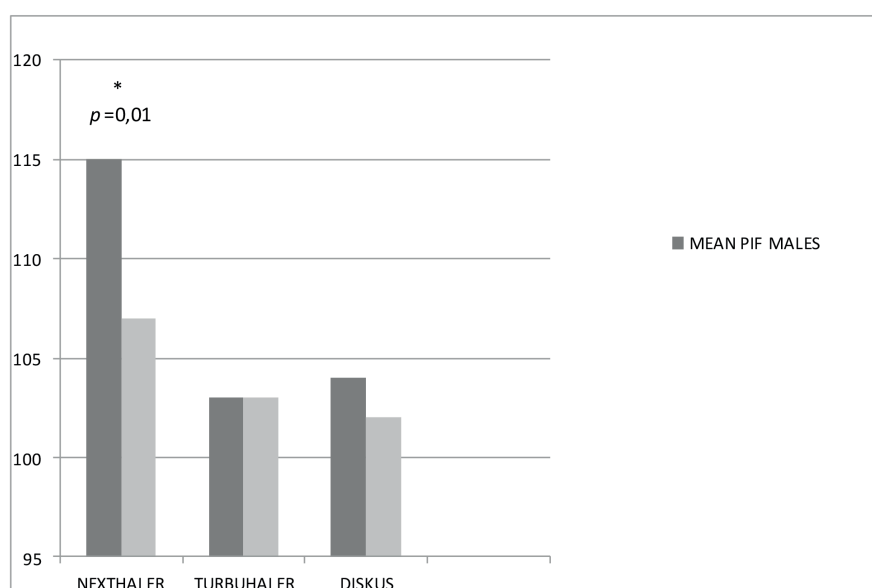


Figure 7. Difference between means PIF of males and females patients.

In 2003 Van Der Palen³⁴ investigated in his study whether patients with asthma or chronic obstructive pulmonary diseases could generate a PIF, which is optimal for the Diskus and the Turbuhaler; in this work the mean PIF through the Diskus resistance was significantly higher than the mean PIF through the Turbuhaler resistance. Furthermore, in this study, it has been found an

important correlation between PIF and MIP, PEF and VC. In our work we have found a mild correlation between PIF and MIP, while the correlation between PIF and the other functional parameters was weak.

Many studies³⁵⁻³⁷ confirmed that when using a DPI the inhalation flow is dependent on the resistance of the device and the patient's inspi-

ratory effort. When patients have a reduced inspiratory capacity a DPI with a low resistance may be a better solution: many works³⁸ have demonstrated that Diskus had the lowest resistance of the DPIs. While in our study³⁹ the mean PIF through the Nexthaler resistance was higher than other PIF generated through other DPIs resistance we have investigated also if we consider separately male and female population.

Conclusions

Inhalation therapy is the mainstay of treatment of patients with COPD. In the last years, significant developments have been achieved in the field of device formulation, but in daily practice, an appropriate inhaler choice should consider not only device related aspects but also patient's pulmonary function and in particular patient's respiratory muscle strength.

Conflicts of interest

The authors declare no conflicts of interest.

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