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Comparative study of breathing parameters of severe asthma patients under biologic therapy through Breezhaler[®], Turbuhaler[®], NEXThaler[®] and Ellipta[®] dry powder inhalers

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Abstract

Background

Patients undergoing biologic therapy need to continue using an inhaler to deliver aerosol drugs via the respiratory tract. In a significant fraction of the patients the improvement of the symptoms and reduction of the inflammation is complemented also by the improvement of the lung function. The aim of this study was to conduct measurements of the inhalation parameters of the patients under biologic therapy through four selected dry powder inhalers to evaluate whether the amelioration of their disease is reflected also in their inhalation performance while using their inhalers. Another aim was to correlate the inhalation parameters through the inhalers with patients' baseline spirometric data.

Methods

50 severe asthmatic patients who were under biologic therapy at the time of the recruitment were included in a single-center cross-sectional clinical study. Normal spirometry and measurement of inhalation curves while inhaling through Breezhaler[®], Turbuhaler[®], NEXThaler[®] and Ellipta[®] was performed.

Results

The mean values of the peak inspiratory flow through the device (PIF_{dev}) were 103.2 L/min, 75.1 L/min, 88.9 L/min and 109.8 L/min for Breezhaler[®], Turbuhaler[®], NEXThaler[®] and Ellipta[®]. All the patients were able to inhale by at least 30 L/min through each device. The mean inspiratory volume (IV) inhaled through the same devices was 2.6 L, 2.3 L, 2.1 L and 2.6 L, respectively. Our results also showed that the main predictors of lung deposition of aerosol drugs (PIF_{dev} and IV_{dev}) correlated well with the corresponding baseline spirometric parameters (PIF and IVC), but also the score of the asthma control test (ACT) in the case of the peak flow. 61-74% of the variance of PIF_{dev} could be explained by the variance of its predictors. The same percentages were 58-87% in the case of IV_{dev} .

Conclusions

The main outcome of this analysis was that in terms of PIF_{dev} and IV_{dev} , asthmatic patients under biological therapy performed as good as healthy subjects and significantly better than COPD patients who were involved in our similar studies in the past. Furthermore, due to the strong correlations shown, it is possible to associate the baseline spirometric parameters with the corresponding parameters through inhaler devices, but predicting power of spirometric parameters is restricted to population level.

Trial registration

The study protocol (BEP-2110/01, 2021 V2) was approved by the National Institute of Pharmacy and Nutrition (OGYÉI/74-3/2022), after the positive evaluation statement of the Ethical Committee of the National Medical Research Council (ETT TUKEB, IV/657- 3 /2022/EKU) registered on 12/02/2022. The registration took place before the first participant was enrolled.

Introduction

Aerosol drugs play a major role in current asthma management. The efficiency the therapy depends on many factors, but delivering the right dose of inhalation drug to the right location within the airways is of key importance. Deposition distribution of drug particles is very much dependent on the breathing parameters of patients during inhalation through the inhaler. These parameters are the result of the patient-device interaction depending not only on the lung capacity of the patient but also on the flow resistance of the device. The value of inhaler resistance exhibits a large inter-device variability, especially in the case of dry powder inhalers (DPI). Therefore, an advantageous airway deposition pattern can be obtained based on the knowledge of the inhalations parameters of individual patients through different devices. Several clinical studies have previously evaluated the breathing performance of asthmatic patients using different DPIs. In many of these studies, healthy subjects and/or patients with COPD were also included. The authors of these studies reported on higher peak flow rates through DPIs (PIF_{dev}) of asthmatics compared to COPD patients (e.g. Malmberg et al., 2014; Seheult et al., 2014; Azouz et al., 2015; Malmberg et al., 2021. Hua et al., 2021). Some other studies compared the PIF_{dev} values of asthmatic patients to the values characteristic of healthy controls (e.g. Prime et al., 2015; Chetta et al., 2021). The outcome of these studies was that while poorly controlled asthmatics had significantly lower peak flow values than their healthy counterparts, well-managed asthma patients performed as good as the healthy controls. The value of PIF_{dev} was mostly a function of the level of asthma control, while severity of obstruction, based on FEV_1 was not a major determinant of peak flow among the well-controlled patients.

As a result of biologic therapies targeting one or more inflammatory mediators or cells in the body (Kavanagh et al., 2022) severe asthmatics who are uncontrolled despite high-dose ICS (inhalation cortico-steroid) and a second controller (and/or systemic cortico-steroids) may have fewer asthma exacerbations and symptoms, fewer asthma-related hospitalizations and decreased use of oral corticosteroids. Moreover, patients controlled on some biologic therapy can have meaningful reductions in ICS dose while maintaining asthma control (Jackson et al, 2024) and even improvement of their lung function (Dominguez-Ortega et al., 2023). It is a very important question whether they are performing better also when inhaling through their inhalers. As most biologics in asthma are relatively new, our knowledge on the breathing parameters of this special group of patients through DPIs is lacking. All the studies mentioned above were either conducted before the introduction of biologic therapy or did not target this patient group. The aim of this study was to investigate inhaler use among patients undergoing biological therapy, with a focus on quantifying their inhalation parameters across various commercially available dry powder inhaler devices. A further objective was to examine the relationship between the breathing parameters recorded during inhalation through these devices and the patients' baseline spirometry values, as well as their demographic and anthropometric characteristics.

Methods

Study design

Severe asthma patients undergoing biological therapy for at least two months (benralizumab, omalizumab or mepolizumab) were recruited in a clinical study conducted at Pulmonology Center of the Reformed Church in Hungary (Törökbálint, Hungary) based on a protocol approved by the National Institute of Pharmacy and Nutrition (OGYÉI/74-3/2022), after the positive evaluation statement of the Ethical Committee of the National Medical Research Council (ETT TUKEB). The research is also a part of a larger study on COPD and asthmatic patients registered on ClinicalTrials.org as the CHOICE study (NCT05445349) on 27/06/2022. 50 adult patients were recruited randomly with equal representation of males and females (25/25). Written consent was obtained from all participants. Among the additional selection criteria, it is worth noting the capability of acting and cooperating and the ability to use the inhaler devices without major handling errors after being educated. The use of any of the DPI devices involved in this study within their current therapy was not a pre-condition of the selection. In addition, the subjects were excluded in the case of incapability of filling the standardized ACT questionnaire (Nathan et al, 2004) or they were unable to properly carry out standard spirometry manoeuvre, or the results of the measurement were not evaluable.

Breathing parameter measurements

Anamnestic, demographic, and anthropometric data were collected prior to the measurements, along with ACT. The assessment began with standard spirometry, during which three consecutive acceptable manoeuvres were performed, and the best curve was selected in accordance with ERS/ATS guidelines (Miller et al., 2005). Subsequently, patients' breathing curves – representing inhaled volume as a function of time – were recorded during inhalation through the four selected dry powder inhaler (DPI) devices: Breezhaler[®], Turbuhaler[®] (Symbicort resistance version), NEXThaler[®] and Ellipta[®]. Before the inhalation through the inhalers the patients were instructed on the manoeuvre based on the descriptions from the summary of product characteristics (SPCs) of the drugs commercialized in each inhaler. It is worth noting that all the selected devices are currently marketed with active pharmaceutical ingredients that have asthma therapy indication. For each device, three measurements were performed, with two-minute rest periods between consecutive efforts. The sequence of inhaler use was randomized for each patient. Both the standard spirometry assessments and the measurements of breathing parameters through DPIs were performed using a mobile handheld digital spirometer (Thor Laboratories, Budapest, Hungary). In the latter case, the spirometer

was positioned between the bacterium filter and the inhaler. The inhalers were attached to the spirometer using customized adapters. The experimental setup can be seen in Figure 1. It was demonstrated that the increase in flow resistance resulting from the use of adapters and the PBF-100-G-M bacterial filter was negligible (see the next section). The inhalers were used in an empty state; therefore, no active substance was inhaled by the patients during the measurements. This precaution was essential to prevent overdosing or interference with ongoing therapy. Importantly, emptying the devices did not significantly affect their internal resistance.

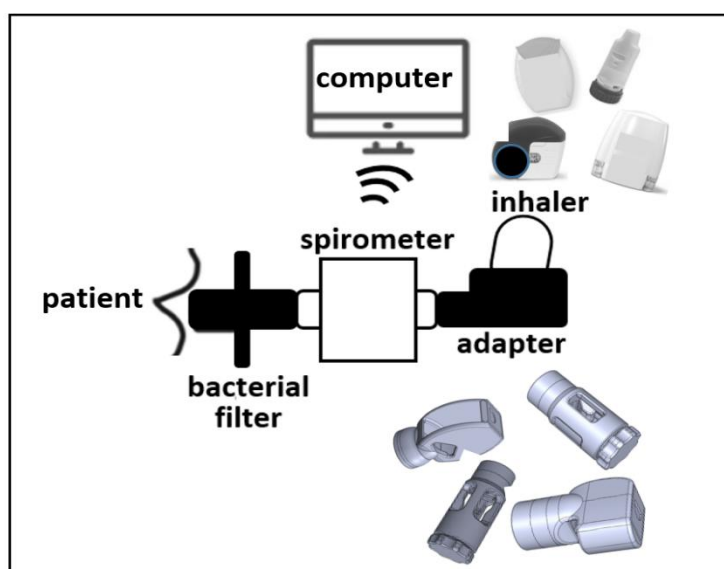


Figure 1. Experimental setup of the measurement of inhalation parameters of the patients through Breezhaler[®], Turbuhaler[®], NEXThaler[®] and Ellipta[®] dry powder inhalers

Among the spirometric parameters, FEV₁(%), FEV₁(L), FEV₁/FVC(%), PIF, PEF, and IVC were measured. The parameters derived from the inhalation curve through the devices were peak inspiratory flow (PIF_{dev}), inhaled volume (IV), inhalation time (t_{in}) and breath-hold time (t_{bh} - measured by a stopwatch) after the inhalation.

Validation of the flow resistance equivalence

Effort has been spent to scientifically validate that the aerodynamic behaviour of the system containing the adapter, emptied inhaler and bacterial filter is similar to that of the filled inhaler without adapters. For this purpose, the experimental apparatus seen in Figure 2, containing a high capacity vacuum pump (HCP6, Copley Scientific) a critical flow controller (TPK 100i, Copley Scientific) and a flowmeter (DFM 2000, Copley Scientific) was set up. The air was

sucked through the filled inhaler and the system used in this study with flow rates of 30, 60, and 90 L/min and the corresponding pressure drops were measured. Three measurements were performed at each flow rate. Flow resistance was calculated as the ratio of the square root of pressure drop to the flow rate. Any difference in terms of resistance between the currently used system and the original filled device was less than 5%.



Figure 2. Experimental setup for the demonstration of flow resistance equivalence

Processing of the measured data

Statistical evaluation of the measured data was carried out by the application of OriginPro 2021, ver. 9.8.0.200 software. Mean values, standard deviations and ranges were determined for each measured quantity. Correlation analyses of PIF_{dev} and IV_{dev} with age, height, BMI, CAT score, PIF, PEF, $FEV_1(\%)$, $FEV_1(L)$, FVC(%), FVC(L), IVC and $FEV_1/FVC(\%)$ were performed. Correlations between different parameters were expressed by Pearson coefficients. The significance threshold was set at $p=0.05$ throughout this study. Best predictor(s) of PIF_{dev} and IV_{dev} were determined by stepwise multivariate linear regression combined with the backward elimination of the least influencing parameter(s).

Results and discussion

Table 1 shows the demographic data, current ACT scores and baseline spirometry parameter values of the asthmatic patients participating in this study. It is worth noting that $FEV_1(\%)$ was higher than 80% in 32% of the patients. At the same time, native PIF was higher than 200 L/min in 54%, and higher than 300 L/min in 26% of the patients, predicting that a high percentage of patients are able to produce a sufficiently high inhalation flow rate through DPI devices.

Table 1. Summary of patient demographics, ACT scores and baseline lung function data. Mean values (first row), standard deviations (second row) and ranges (third row) for the population of 50 patients are provided. BMI – body mass index; FEV₁ - expiratory volume at the end of the first second of forced exhalation; FVC – forced vital capacity; PIF – peak inhalation flow; PEF – peak exhalation flow; IVC – inspiratory vital capacity

Age (years)	Gender (F:M %)	BMI (kg/m ²)	ACT	FEV ₁ (L)	FEV ₁ (%)	FVC (L)	FVC (%)	FEV ₁ /FVC (%)	PIF (L/min)	PEF (L/min)	IVC (L)
59.7 ±13.2	50:50	28.5 ±6.0	21.3 ±3.6	2.1 ±0.8	69.8 ±19.9	3.0 ±1.0	80.2 ±18.4	69.7 ±11.8	230.7 ±117.1	295.1 ±137.9	2.8 ±1.0
20-79		18.3-49.3	12-25	0.5-3.9	22-108	1.2-4.9	35-120	41.7-99.4	49.8-497.4	66-617	0.5-4.9

Figure 3 depicts the values of peak inspiratory flow and inhaled volume measured when the patients inhaled through the four selected DPI devices. As the figure demonstrates, mean PIF_{dev} was higher for Breezhaler® (103.2 L/min) and Ellipta® (109.8 L/min) and lower for Turbuhaler® (75.1 L/min) and NEXThaler® (88.9 L/min). This was a result of the higher flow resistance of the last two inhalers. More importantly, all the patients under biological therapy were able to exceed 30 L/min, which is considered the lower limit for the successful use of a DPI. Moreover, all the patients were able to exceed 35 L/min through NEXThaler®, which is a threshold for the release of the drug controlled by the built in breath actuated mechanism (BAM, Corradi et al, 2014). The mean values of PIF_{dev} in this study are also higher than those characteristic of COPD patients who were the subjects of our previous studies, except for Turbuhaler®. In our recent work the mean PIF_{dev} of COPD patients was 68.4 L/min through NEXThaler® and 78 through Ellipta® (Farkas et al., 2024). Similarly, the mean PIF_{dev} values of COPD patients were 75.1 L/min and 91.4 L/min for Turbuhaler® and Breezhaler® (Farkas et al., 2019). Moreover, current peak inspiratory flow values are comparable to the values characteristic of healthy subjects, even exceeding them in some cases. The average of three inhalation manoeuvres of healthy persons was 102.3 L/min for Breezhaler®, 72 L/min for Turbuhaler®, 71.8 for NEXThaler® and 82.8 L/min for Ellipta® (Farkas et al., 2023).

Regarding the inhaled volume, current average values are categorically higher than the similar values of COPD patients reported in the same publications as above (Breezhaler®: 2.6 L versus 1.9 L; Turbuhaler®: 2.3 L versus 1.8 L; NEXThaler®: 2.1 L versus 1.5 L and Ellipta®: 2.6 L versus 1.5 L). These results are of high importance as airway deposition increases with the increase of the inhaled volume (Legat and Naus, 1997). Another aspect worth noting is that the

number of female and male participants was equal in this study, while males were overrepresented in the previous COPD studies. Considering that men had higher PIF_{dev} and IV_{dev} values than women (according to the two-sample t-test, the differences between the mean values of PIF_{dev} and IV_{dev} corresponding to the two groups were statistically significant for all the four inhaler devices), the above statements become even more underpinned.

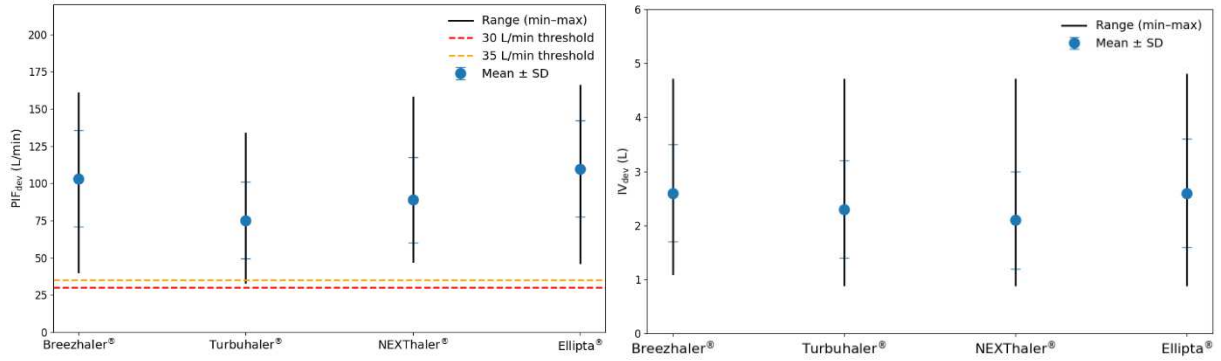


Figure 3. Boxplots of measured breathing parameter values through Breezhaler®, Turbuhaler®, NEXThaler® and Ellipta® DPIs. Mean values, standard deviations and ranges for the population of 50 patients are marked. PIF_{dev} – peak inspiratory flow while inhaling through the device; IV_{dev} – volume of air inhaled through the device

Summarizing the results of standard spirometry and breathing curve measurements through inhaler devices (Table 1 and Figure 3), it can be stated that most of severe asthma patients undergoing biologic therapy have relatively good breathing capacity both against nearly zero resistance (spirometer) and against DPI devices with different flow resistances. It is worth emphasizing that while baseline spirometric parameters are measured for every asthmatic, inhalation curves through the inhalers are not routinely recorded. An important question is whether the results of standard spirometry are associated with the corresponding values through inhaler devices. Another question is whether the association has predicting power, and whether a good prediction can be made only at population level or even at individual level.

Practically, in terms of mathematics this implied a systematic correlation analysis between the main parameters through inhalers and the known demographic and routinely measured breathing parameters (datasets whose basic statistics are presented in Table 1, except gender). The final aim was to find the main predictors of PIF_{dev} and IV_{dev} , however this needed to be preceded by multi-collinearity checks. A pairwise cross-correlation analysis between the parameters in Table 1 revealed high correlation coefficients (>0.9) between different lung volumes on the one hand (e.g. $FVC(L)-FVC(\%)$, $FEV_1(L)-FEV_1(\%)$, $FVC(L)-FEV_1(\%)$, $IVC-FVC(L)$, $IVC(FVC(\%))$, $IVC-FEV_1(\%)$, $PIF-PEF$ and $FVC(\%)-FEV_1(\%)$), and obviously between BMI and height. By the same token, patient age showed moderate inverse correlation

with lung function data (0.4-0.5), while ACT was not correlated with any of the studied parameters. Since strong collinearities can lead to low statistical significance and inflated standard errors, the number of predictors was reduced to IVC, PIF, BMI, ACT and age. Basically, the Principal Component Analysis stood on the basis of parameter reduction, but is worth noting that since both PIF_{dev} and IV_{dev} , are inhalation parameters, IVC and PIF were preferred against the corresponding exhalation parameters. As the next step, the correlation of the main parameters characterizing the inhalation through the selected DPIs (PIF_{dev} and IV_{dev}) with the remaining parameters (IVC, PIF, BMI, ACT) was analysed. Figure 4 presents the graphical representation of Pearson coefficients as a heatmap.

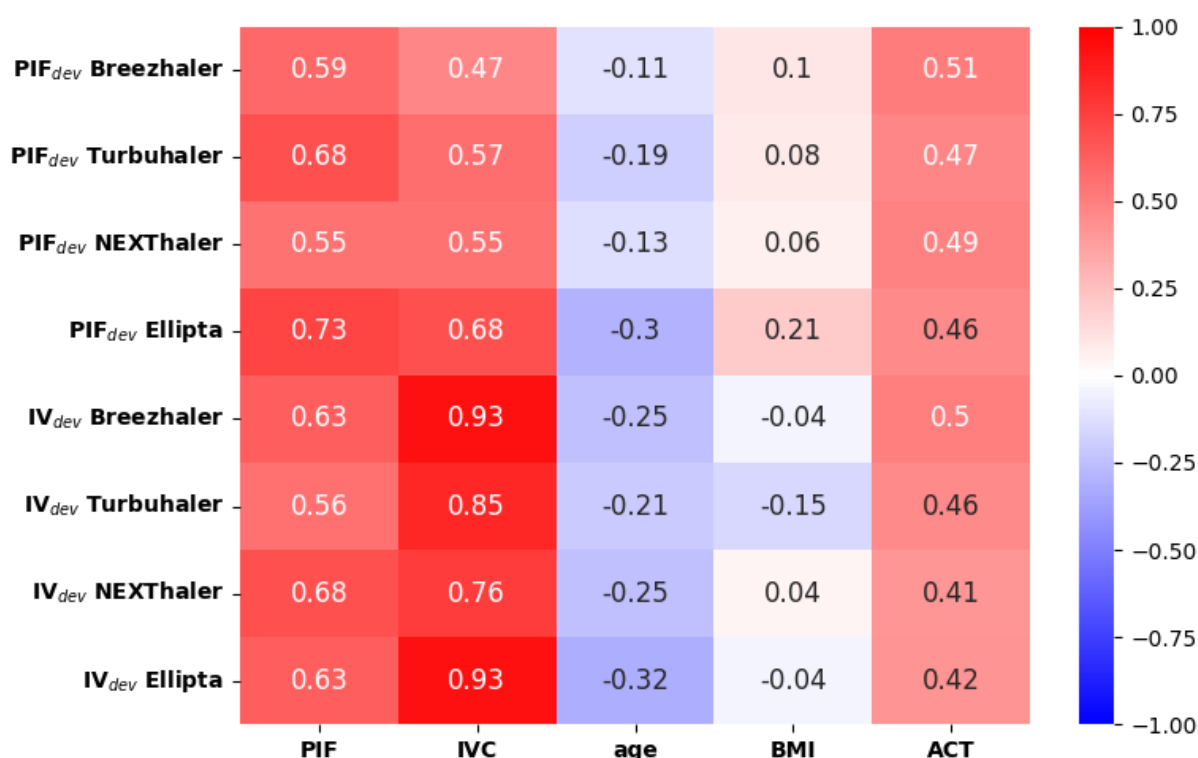


Figure 4. Pearson correlation coefficients (r) of peak inspiratory flow (PIF_{dev}) and inhaled volume (IV_{dev}) values through different dry powder inhalers and standard baseline peak inspiratory and expiratory flows (PIF and PEF), inspiratory vital capacity (IVC), expiratory volume in the first second of forced exhalation (FEV_1 in % and L), forced vital capacity (FVC in % and L), FEV_1/FVC (%), patient's age, body mass index (BMI), height (h) and ACT score

As the data in Figure 4 demonstrate, both the strength of correlation and its significance were device specific, but regularly both PIF_{dev} and IV_{dev} correlated well with the native PIF and IVC, to a less extent with ACT, insignificantly with BMI and insignificantly or only weakly with age. As the quantities behind the heatmap may still correlate with each other, it is essential to determine the main predictors of PIF_{dev} and IV_{dev} and the degree of their predictability. The

application of a stepwise multiple linear regression and a backward elimination study resulted in the main predictors demonstrated in Table 2. Besides the device specific main predictors of PIF_{dev} and IV_{dev} , Table 2 shows the values of R^2 as the indicator of the predictability and the R^2 values associated with single predictors. In addition, the best fit equations are also provided. According to the table, the main predictors of PIF_{dev} are the native PIF and ACT score, that is a physiological actor and a symptomatic factor. For instance, 53% of the variation of PIF_{dev} through Ellipta[®] can be explained by the variation of the baseline PIF. Adding the second predictor (ACT), in addition to PIF, results in 59% variance of PIF_{dev} explainable by the variance of the two parameters. Regarding the strength of each predictor, the analysis of standardized regression coefficients has shown that PIF and ACT are approximately equally important in predicting the peak flowrate through the inhalers. An even better prediction can be made on the expected value of IV_{dev} based on native spirometry data as the values of R^2 span between 0.58-0.87. However, the only mean predictor of IV_{dev} is IVC.

Table 2. The results of the stepwise multivariate linear regression and backward elimination technique providing the best predictors of peak inspiratory flow and inhaled volume through the four DPIs. Note that the only main predictor of IV_{dev} is IVC, thus the corresponding values in columns 3 and 5 are the same

Breathing parameter through DPI	Inhaler name	Main predictors (R^2)	Predicting equation	Single predictors (R^2)
PIF_{dev} (L/min)	Breezhaler [®]	PIF, ACT (0.45)	$0.120 \times PIF + 2.507 \times ACT + 23.587$	PIF (0.35), ACT (0.26)
	Turbuhaler [®]	PIF, ACT (0.51)	$0.119 \times PIF + 1.545 \times ACT + 15.956$	PIF (0.46), ACT (0.26)
	NEXThaler [®]	PIF, ACT (0.42)	$0.090 \times PIF + 2.242 \times ACT + 22.123$	PIF (0.30), ACT (0.24)
	Ellipta [®]	PIF, ACT (0.59)	$0.161 \times PIF + 2.267 \times ACT + 24.904$	PIF (0.53), ACT (0.21)
IV_{dev} (L)	Breezhaler [®]	IVC (0.87)	$0.833 \times IVC + 0.259$	IVC (0.86)
	Turbuhaler [®]	IVC (0.72)	$0.745 \times IVC + 0.239$	IVC (0.72)
	NEXThaler [®]	IVC (0.58)	$0.650 \times IVC + 0.234$	IVC (0.58)
	Ellipta [®]	IVC (0.87)	$0.833 \times IVC + 0.331$	IVC (0.87)

Summarizing the results of multivariate regression analysis, the best predictors of PIF_{dev} and IV_{dev} are PIF and IVC, respectively. However, the degree of predictability of PIF_{dev} can be improved to some extent (by a few percent) in all the cases by considering the second best predictor. Figure 5 depicts the PIF_{dev} - PIF and IV_{dev} - IVC linear relationships for the four devices in the focus of this study. Each data point corresponds to one asthmatic patient.

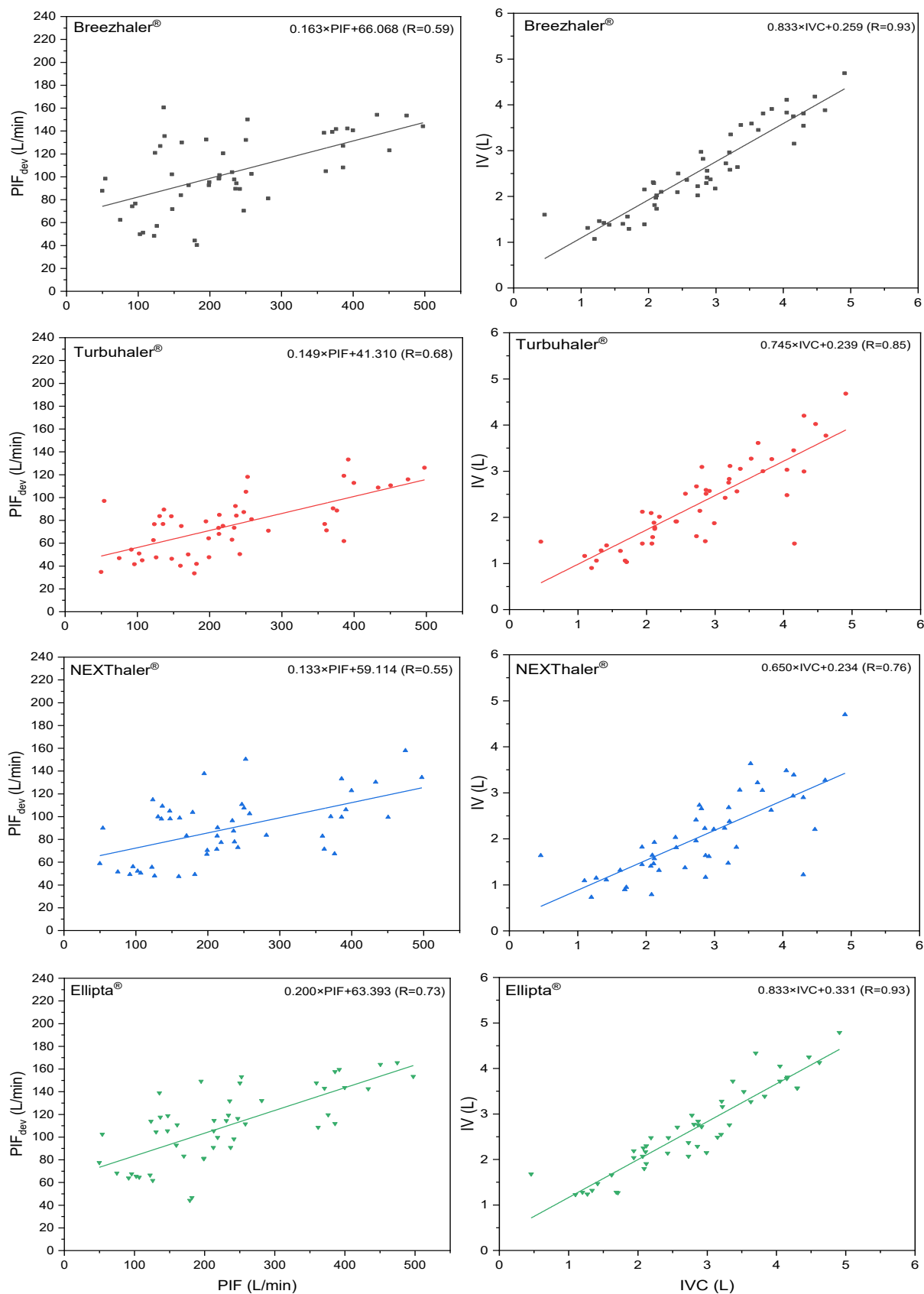


Figure 5. Relationship between PIF_{dev} and PIF (left panels), and IV_{dev} and IVC (right panels) based on standard spirometry and measurements through Breezhaler®, Turbuhaler®, NEXThaler® and Ellipta® dry powder inhalers. R-Pearson coefficient

The correlation (Pearson) coefficients are comparable to those characterizing the groups of COPD patients, meaning that the expected values of the important determinants of aerosol drug deposition (PIF_{dev} , IV) can be predicted at a similar level. In our previous studies on COPD patients the Pearson coefficients for the PIF_{dev} -PIF relationship were 0.60, 0.57, 0.57 and 0.71 in the cases of Breezhaler[®], Turbuhaler[®], NEXThaler[®] and Ellipta[®], respectively (Farkas et al., 2019; Farkas et al, 2024). However, the predictability could be improved in the present case by considering the ACT score, which proved to be one of the main determinants of PIF_{dev} . It is worth noting that a similar attempt was not done by us to include CAT score in the regression analysis of PIF_{dev} of COPD patients. By the same token, we are also not aware of any publication considering ACT or CAT for such purpose, thus the present result can be considered as a novelty.

To analyse whether the predictions can be made only at population level or at the level of individuals, Bland-Altman analysis has been performed for both peak inspiratory flows and inhaled volumes. Figure 6 depicts the results of these analyses. The combined Bland–Altman plot illustrates the agreement between predicted and measured device-specific peak inspiratory flow (PIF_{dev} , left panel) and inhaled volume (IV_{dev} , right panel) across all four inhaler devices. Each device is represented with a distinct colour, allowing direct visual comparison of prediction accuracy and error structure.

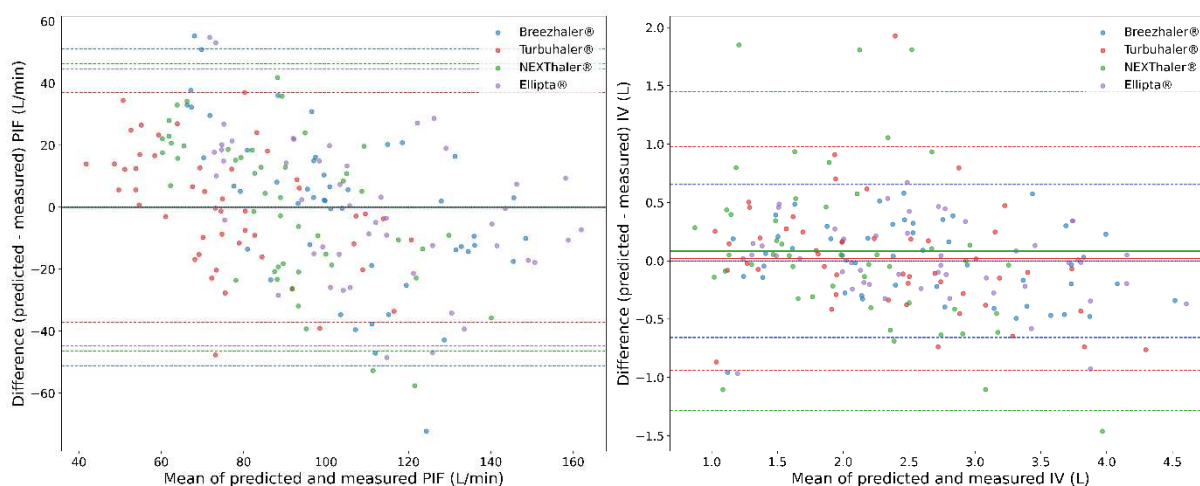


Figure 6. Combined Bland–Altman plot of the predicted and measured device-specific peak inspiratory flow (PIF_{dev} , left panel) and inhaled volume (IV_{dev} , right panel) across all four inhaler devices

Across all four inhaler devices, Bland–Altman analyses for both PIF and IV revealed small mean biases but wide limits of agreement and significant proportional bias. These findings indicate that although the spirometry-based regression models provided good population level estimates, they did not provide sufficiently accurate individual-level predictions of device-specific inspiratory performance. Although average agreement appears acceptable, the large inter-individual variability and systematic under- or overestimation across the performance range limit the clinical applicability.

Conclusions

This study enabled the assessment of the use of dry powder inhalers by severe asthma patients who presently are treated by one of the available biologics, and the establishment of relationships between the main predictors of the success of inhaler use and the corresponding baseline spirometric parameters. The results of the research demonstrated that patients undergoing biologic therapy are able to achieve breathing parameters that can ensure a successful inhaler use. This work also revealed that baseline spirometric parameters, together with ACT score, can reasonably predict the inhalation parameters patients achieve when using different DPI devices at population level, but individual predictions had high levels of uncertainty.

Declarations

Abbreviations

Not applicable.

Ethics approval and consent to participate

The study protocol (BEP-2110/01, 2021 V2) was approved by the National Institute of Pharmacy and Nutrition (OGYÉI/74-3/2022), after the positive evaluation statement of the Ethical Committee of the National Medical Research Council (ETT TUKEB, IV/657- 3 /2022/EKU). Informed, written consent was obtained from all participants. All the measurements and the related work were performed in accordance with the Declaration of Helsinki. The registration took place on 12/02/2022, before the first participant was enrolled. The study was registered on ClinicalTrials.org under number NCT05445349 on 27/06/2022.

Consent for publication

Not applicable.

Availability of data and materials

Research data can be found in the *zenodo* repository: <https://zenodo.org/records/22690922>

Competing Interests

Hereby, the authors declare that they gave no competing interests.

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Not applicable.

Authors' contributions

All the authors have approved the manuscript for submission.

ÁF, BS, GG, EK, IR and BS conceptualization; ÁF and AH device validation; IR, NI and BH breathing profile measurements; ÁF, GG, BS, AH and LS data management, ÁF, BS, IR, HB, NI and EK statistical evaluation; ÁF and LS numerical simulations; BH, NI, GG, IR writing the main manuscript text, GG, LS, EK preparation of the figures; All authors reviewed the manuscript.

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