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Inappropriate Peak Inspiratory Flow Rate in the Patients with Stable Chronic Obstructive Pulmonary Disease in Korea

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Abstract

Background: While inhalation therapy efficacy hinges on attaining proper peak inspiratory flow rate (PIFR), the prevalence of inappropriate PIFR among patients with chronic obstructive pulmonary disease (COPD) remains unstudied in Korea. This study aimed to assess the prevalence of inappropriate PIFR, its correlation with COPD assessment test (CAT) scores, and factors associated with suboptimal PIFR.

Methods: We enrolled 108 patients with COPD who had been using the same inhaler for at least 1 year without exacerbations. PIFR was measured using an inspiratory flow meter (In-Check DIAL G16). Demographic, clinical, pulmonary function, and CAT score data were collected. Inappropriate was defined as PIFR <60 L/min for dry power inhaler (DPI) users, and >90 L/min for aerosol device users.

Results: The cohort comprised 87 (80.6%) men, mean age 71.0±8.5 years, with mean post-bronchodilator forced expiratory volume in 1 second of 69.1%±1.8% predicted. Twenty-nine (26.9%) used aerosol devices only, 76 (70.4%) used DPIs only, and three (2.8%) used both. Inappropriate PIFRs were found in 17.2% of aerosol device users, and 42.1% of DPI users. CAT scores were significantly higher in the inappropriate PIFR group than in the appropriate PIFR group (11.2±7.7 vs. 7.5±4.9, p=0.003). In DPI users, female, shorter height, lower body weight and maximal voluntary ventilation (MVV) were associated with inappropriate PIFR.

Conclusion: The prevalence of inappropriate PIFR among patients with COPD is 17.2% for aerosol device users, and 42.1% for DPI users. Suboptimal PIFR correlates with female gender, shorter stature, lower weight and MVV in DPI users.

Keywords: Inspiratory Flow; Dry Power Inhaler; Chronic Obstructive Pulmonary Disease; In-Check Dial; Inhaler; Peak Inspiratory Flow Rate

Introduction

Inhalation therapy plays a vital role in the treatment of chronic obstructive pulmonary disease (COPD). However, the effectiveness of the inhalation therapy depends on the proper deposition of the inhaled drug in the targeted small airways, which can be affected by various factors: the patient, device, and formulation of the drug[1]. Ongoing development of inhaler devices and drug formulations has made it possible to achieve reliable drug delivery, when used correctly. However, despite the availability of educational tools and assistive devices, the inhaler technique used by patients with COPD has not improved significantly over time[2]. Critical errors in the steps dealing with the inhalation device are common, and this is a huge problem linked

to negative treatment outcomes[3].

Each type of inhaler device has its own way of being used properly. In general, aerosol inhalers, such as the pressured metered-dose inhaler (pMDI) and soft mist inhaler (SMI), require "push-inhalation coordination," with a slow and deep inhalation by the patient to achieve optimal drug delivery[4]. This is owing to the device generating its own aerosol, and so a slower inhalation rate is required to ensure that the drug deposits in the peripheral airways, since fast inhalation will increase the velocity of the drug particles, thus increasing impaction in the oropharynx[5]. However, dry power inhalers (DPIs) require a fast and deep inhalation to "suck up" the drug in the inhaler device. A fast inhalation rate generates a large internal turbulent force in the inhaler device, which is required to break up the formulation of the metered dose to produce particles of a size distribution that will penetrate the peripheral airways[6].

The optimal peak inspiratory flow rate (PIFR) is an important factor to achieve successful inhaler use. The PIFR, the measure of a patient's inspiratory effort, can be used to assess a patient's ability to generate an adequate inspiratory flow rate from DPIs, and it is suggested that an under-PIFR may result in ineffective inhalation of the medication. DPIs act as breath-actuated devices, many of which require the patient to generate a sufficient PIFR to disaggregate the powder into particles of <5 μm diameter, which can then be inhaled into the lower respiratory tract. The internal resistance of a device, and hence the flow required to overcome this resistance, varies with the DPI design[7]. In contrast, in the case of aerosol inhalers, an over-PIFR leads to drug deposition in the oropharynx or large airway, and not the targeted peripheral lung. Therefore, an optimal PIFR is a major requirement of successful inhaler use in both aerosol inhaler and DPI users[4]. Hence, an inappropriate PIFR includes both cases of patients who have under-PIFR among the DPI users, and those who have over-PIFR among the aerosol inhaler users.

We estimated the prevalence of inappropriate PIFR among patients with COPD and evaluated the possible associated factors with inappropriate PIFR. We also hypothesized that ineffective inhalation of medications due to inappropriate PIFR could result in a poor quality of life in patients with COPD. Therefore, we investigated the association of inappropriate PIFR with a COPD assessment test (CAT) score.

Materials and Methods

Patients with COPD who have been using the same inhalation device for at least 1 year without an acute exacerbation (AE) in the previous year were included. The patients were eligible for inclusion in the study if they were ≥40 years of age and had stable moderate to very severe (forced expiratory volume in 1 second [FEV_1] <80% of predicted) COPD. The patients were excluded from the study if they were unable or unwilling to provide informed consent, had experienced COPD AE within the last 1 year, were currently hospitalized, or were currently residing in a long-term care facility. The PIFR was measured with an In-Check DIAL G16 (Clement Clarke International Limited, London, UK), which had a selectable resistance by a trained nurse to simulate the resistance according to the device[8]. The demographic data, pulmonary function test results, and CAT score were recorded[9]. Maximal voluntary ventilation (MVV) was measured in the sitting position to breathe as rapidly and deeply as possible through a spirometer for 15 seconds, and the volume of air moved over that period of time was calculated.

We analyzed the data according to the type of inhaler device, and by aerosol inhaler users and DPI users. The cut-off of the optimal PIFR for aerosol inhaler users was set at ≤90 L/min, and that for the DPI group was set at ≥60 L/min. Though there is still discussion about the effectiveness of PIFR ranging 30 to 60 L/min, PIFR ≥60 L/min is generally believed to be the optimal flow for most dry power inhalation devices[10-12]. Additionally, we divided the DPI users into the optimal group, who had PIFR high enough to overcome the device's unique internal resistance, and the suboptimal group, who had that below the device's unique internal resistance[13]. The patients who used more than two different devices could belong to the appropriate group when they had a sufficient PIFR to use both inhalers properly.

The data was collected from September 1, 2020 to February 28, 2021. Data collection and analysis were approved by the Institutional Review Board of Keimyung University Dongsan Hospital (DSMC 2023-03-061).

1. Statistical analysis

The descriptive statistics were reported using the mean and standard deviation for continuous variables, and frequency and percentages for categorical variables. The differences between the two groups were tested using independent sample t-tests for continuous variables, and chi-squared tests for categorical variables. To determine the associated factors with the PIFR, a correlation analysis was performed using a Pearson analysis and regression modeling analysis. The analyses and statistical tests were conducted us-

ing IBM SPSS Statistics version 29 software (IBM SPSS Inc., Armonk, NY, USA). Statistical significance was defined as p<0.05.

Results

1. Baseline characteristics

We collected 108 patients, of whom 87 (80.6%) were men, with the mean age being 71.0±8.5 years old. The mean post-bronchodilator FEV_1 was 69.1%±18.4% of the predicted value. The types of inhalers consisted of a Breezehaler (Norvatis, Basel, Switzerland) in 40 (33.9%), Respimat (Boehringer Ingelheim, Ingelheim, Germany) in 32 (27.1%), and Ellipta (GSK, London, UK) in 29 (24.6%) patients. According to the medication, a dual bronchodilator therapy that combined a long-acting beta-agonist and long-acting muscarinic antagonist was prescribed in 66 (61.1%) patients, and 21 (19.4%) patients were prescribed an inhaler that include an inhaled corticosteroid (Table 1).

Except for three people using multiple types of inhalers, there were 29 (27.0%) aerosol inhaler users and 76 (70.4%) DPI users. Of the total 29 patients using a pMDI or SMI, five (17.2%) had an inappropriate PIFR (>90 L/min). Of the total 76 DPI users, 32 (42.1%) had a suboptimal PIFR (<60 L/min). Of the three patients who used two different mechanism inhalers, one patient used both types of inhalers properly. Others had too high a PIFR for the aerosol device, or too low a PIFR for the DPIs.

Table 1. Baseline characteristics

Characteristic	Value
Total	108
Sex, male:female	87:21
Age, yr	71.0±8.5
BMI, kg/m^2	23.2±2.9
Duration of the diagnosis COPD, yr	7.0±3.9
Duration of the using inhalers, yr	3.4±3.1
Type of inhaler device (total 118)	
Breezhaler	40 (33.9)
Respimat	32 (27.1)
Ellipta	29 (24.6)
Handihaler	6 (5.1)
Diskus	4 (3.4)
Turbuhaler	4 (3.4)
pMDI	2 (1.7)
Genuair	1 (0.8)
Pulmonary function test	
PostBD FEV_1/FVC	57.1±9.6
PostBD FEV_1, % of predicted	69.1±18.4
PostBD FVC, % of predicted	80.9±16.7
MVV, % of predicted	53.9±17.6
TLC, % of predicted	108.2±20.4
RV, % of predicted	134.4±40.1
RV/TLC	50.5±10.3
DLCO/VA	89.2±27.2
CAT score	8.8±6.3
Type of medication	
LAMA	18 (16.7)
LABA	3 (2.8)
LABA/LAMA	66 (61.1)
ICS/LABA	4 (3.7)
ICS/LABA/LAMA	17 (15.7)

Values are presented as mean±standard deviation or number (%).
BMI: body mass index; COPD: chronic obstructive pulmonary disease; pMDI: pressured metered-dose inhaler; BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MVV: maximal voluntary ventilation; TLC: total lung capacity; RV: residual volume; DLCO: diffusion lung carbon oxide; VA: alveolar volume; CAT: COPD assessment test; LAMA: long-acting muscarinic antagonist; LABA: long-acting beta-agonist; ICS: inhaled corticosteroid.

2. Optimal PIFR vs. suboptimal PIFR

There were 69 (63.9%) patients who had optimal PIFR according to the type of device, and 39 (36.1%) patients who had suboptimal PIFR. The CAT score of the optimal PIFR group was significantly lower than that of the suboptimal PIFR group (7.5±4.9 vs. 11.2±7.7, p=0.003).

3. Subgroup analysis of the aerosol inhaler device users (n=29)

Of the 29 total patients using a pMDI or SMI, five (17.2%) patients had a PIFR of over 90 L/min. The CAT score did not differ between the optimal PIFR and suboptimal PIFR groups (p=0.295).

4. Subgroup analysis in the DPI users (n=76)

Of the 76 total patients using DPIs, 32 (42.1%) had a suboptimal PIFR (PIFR <60 L/min). Females were prevalent in the suboptimal PIFR group (37.5% vs. 9.1%, p=0.003). The patients in the suboptimal PIFR group were significantly shorter and had lower body weight than those in the optimal PIFR group. The MVV of the optimal PIFR group was higher than that of the suboptimal PIFR group (65.1±23.2 vs. 42.4±13.4, p<0.001). The CAT score was significantly higher in the suboptimal

PIFR group (10.4±6.7 vs. 7.4±4.0, p=0.029). Comparing scores for each item, differences were observed between the two groups in terms of the activity and confidence (Table 2).

Considering the resistance of each device, 18 (23.7%) patients had a suboptimal PIFR. Compared to that in the optimal group, the CAT score was higher in the suboptimal group (11.1±6.8 vs. 7.9±4.8, p=0.034). Females were prevalent in the suboptimal group (38.9% vs. 15.5%, p=0.034) (Table 3).

5. Factors associated with the PIFR

In the DPI users, the PIFR was negatively correlated with age (r=−0.285, p=0.013), and positively correlated with height (r=0.346, p=0.002), weight (r=0.271, p=0.018), and MVV (r=0.438, p<0.001). No predictive factor of optimal PIFR was found in the multiple logistic regression modeling in this study.

Discussion

Among the patients with stable COPD in this study, 42.1% of the patients using DPIs and 17.2% of the patients using aerosol inhalers had inappropriate PIFR, and the patients with inappropriate PIFR had a significantly higher CAT score than those with appropriate PIFR. Suboptimal PIFR was associated with female gender, shorter stature, lower body weight, and lower MVV in the DPI users.

The ability to generate optimal inspiratory flow is essential for effective aerosol drug delivery from DPIs, because it requires a powerful forced inspiratory effort to overcome the device's unique internal resistance to appropriately disperse the drug and deliver it to the targeted small airways[14]. Ineffective drug delivery to the targeted small airways due to suboptimal PIFR could result in a worse clinical outcome. Suboptimal PIFR was associated with higher CAT score, as shown in this study, and was also associated with frequent exacerbation and shorter time to the COPD AE, as compared to optimal PIFR[15,16], and it is well known that a COPD AE is related to mortality from COPD[17,18].

We have found that suboptimal PIFR was observed in 42.1% of the DPI users; however, this study includ-

Table 2. Subgroup analysis of the DPI users (n=76)

Variable	PIFR ≥60 L/min	PIFR <60 L/min	p-value
Total	44 (57.9)	32 (42.1)	-
Female sex	4 (9.1)	12 (37.5)	0.007
Age, yr	70.0±7.2	73.3±8.4	0.065
PIFR, L/min	74.5±9.1	44.5±11.0	<0.001
CAT score (total)	7.4±4.0	10.4±6.7	0.029
Cough	1.1±0.8	1.2±1.1	0.766
Phlegm	1.2±1.0	1.4±1.2	0.414
Chest tightness	0.8±1.0	1.0±1.2	0.425
Breathlessness	2.3±1.3	2.8±1.5	0.111
Activities	0.2±0.5	0.8±1.3	0.024
Confidence	0.2±0.6	0.8±1.3	0.032
Sleep	0.7±1.2	1.1±1.5	0.244
Energy	0.9±1.2	1.4±1.6	0.150
PostFEV_1, %	68.2±18.2	67.1±18.7	0.793
FEV_1/FVC	56.7±10.4	56.4±9.7	0.892
MVV, L/min	65.1±23.2	42.4±13.4	<0.001
Height, cm	164.3±7.0	158.4±8.6	0.002
Weight, kg	63.5±7.8	58.4±11.3	0.032
BMI, kg/m^2	23.5±2.5	23.2±3.6	0.645

Values are presented as number (%) or mean±standard deviation.
DPI: dry powder inhaler; PIFR: peak inspiratory flow rate; CAT: COPD assessment test; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MVV: maximal voluntary ventilation; BMI: body mass index.

Table 3. Subgroup of the DPI users according to the device-specific internal resistance (n=76)

Variable	Optimal PIFR	Suboptimal PIFR	p-value
Total	58 (76.3)	18 (23.7)	
Female sex	9 (15.5)	7 (38.9)	0.034
Age, yr	70.6±7.7	74.1±8.1	0.167
PIFR, L/min	68.1±14.5	41.9±12.5	<0.001
CAT score (total)	7.9±4.8	11.1±6.8	0.034
Cough	1.1±0.9	1.1±1.2	0.970
Phlegm	1.2±1.0	1.6±1.2	0.193
Chest tightness	0.9±1.1	0.9±1.0	0.782
Breathlessness	2.4±1.3	2.9±1.6	0.234
Activities	0.3±0.8	0.8±1.4	0.128
Confidence	0.3±0.8	0.8±1.5	0.126
Sleep	0.7±1.2	1.3±1.6	0.104
Energy	1.0±1.3	1.4±1.7	0.223
PostFEV_1 , %	67.3±17.7	69.4±21.2	0.942
FEV_1/FVC	67.7±17.5	68.1±21.3	0.303
MVV, L/min	60.0±23.0	42.7±16.0	0.006
Height, cm	162.6±7.2	159.2±10.6	0.209
Weight, kg	62.6±8.4	57.3±12.5	0.043
BMI, kg/m^2	23.7±2.7	22.5±3.7	0.168

Values are presented as number (%) or mean±standard deviation.
DPI: dry powder inhaler; PIFR: peak inspiratory flow rate; CAT: COPD assessment test; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MVV: maximal voluntary ventilation; BMI: body mass index.

ed patients who were not hospitalized due to a COPD AE in the previous year and had been using the same device for at least 1 year, as compared to the other investigators who reported a similar prevalence of 38.8% to 52.0% in patients including patients admitted with a COPD AE[19-22]. Moreover, this study revealed that one of the five patients being prescribed with a DPI could not reach the threshold of the minimal PIFR required flow that could turn the powder into particles suitable for absorption in the peripheral lungs. A PIFR mismatch with the prescribed inhalers was recently reported among COPD cohorts with variable prevalence ranging 32% to 77%[23]. This study was conducted at a single center; therefore, the generalizability of the results is limited; however, this suggested that suboptimal PIFR in patients with COPD is relatively common, even if they did not have an AE in a previous year, or their symptom burden was not higher. Even patients with stable COPD without a history of AE or those with low CAT scores, having suboptimal PIFR could increase the risk of AE and symptom burden. Therefore, we suggest measuring the PIFR and CAT score in COPD with stable COPD to obtain objective understanding of the situation.

Since the optimal delivery of an inhaled drug is dependent on the patient achieving optimal PIFR during inhalation, the patients with COPD prescribed with a DPI should have their PIFR checked through the inhaler before the prescription. Additionally, patients prescribed with an aerosol inhaler should be trained to inhale steadily and deep with lower PIFR. However, the measurement of PIFR against simulated resistance of the inhaler is not frequently performed in clinical practice, due to it being time consuming and to equipment limitations, and the cost is usually considered. Although there are no defined clinical predictors of suboptimal PIFR, female gender has been reported as a significant clinical predictor in the prior results of studies of suboptimal PIFR for COPD, when measurements of the PIFR are unavailable in clinical practice[20,23]. Also, small stature was observed in the suboptimal PIFR group[24]. Further, there are some discrepancies about the relationship between the PIFR and spirometric factors, such as forced vital capacity, FEV_1, and MVV[22,25]. Although PIFR and MVV assess different aspects of

lung function and are not directly interchangeable, both PIFR and MVV can provide valuable information about assessing the impact of respiratory muscle weakness. Given that females with shorter height and lower body weight could have greater probability of having lower PIFR, as shown in this study, for those patients, a DPI with lower resistance or an aerosol inhaler may be a better alternative, based on several studies up to date.

This study had several limitations. (1) Given the cross-sectional design of this study, we could not confirm the causal effect of the PIFR on the quality of life in patients with COPD. (2) This study faced challenges in deriving significant results from multiple logistic regression analysis looking for association between inappropriate PIFR and predictive clinical factors, due to its small sample size, short-term nature, and conduct in a single institution. Although there is a lack of practical and standardized recommendations to measure the PIFR, we followed the guidance of the In-Check DIAL G16 manufacturer[26].

Despite these various limitations, there are several strengths that are worth considering. (1) Few studies measuring the PIFR in patients with COPD have been performed in Korea. As far as we know, this is the first study to measure the PIFR and analyze its effect on the quality of life in Korean patients. (2) This study can reflect real clinical practice, because we included patients who visited our out-patient clinic. (3) Since the well-trained nurse carefully observed the entire process of handling the devices for each patient, we could minimize the effect of the factors that could affect the lung deposition of a drug, such as exhalation before the use of the inhaler, sealing the lips, and holding the breath after inhalation.

We showed that inappropriate PIFR was relatively common among stable patients with COPD and was associated with poor quality of life. Female, shorter stature, and lower body weight and MVV were associated with suboptimal PIFR in DPI users.

Authors' Contributions

Conceptualization: Kim HJ, Park JS. Methodology: Youn SH, Park SH, Kim MA. Formal analysis: Youn SH, Kim HJ. Data curation: Park JS, Park SH, Kwon YS, Kim MA. Writing - original draft preparation: Youn SH, Kim HJ. Writing - review and editing: Park JS, Park SH, Kwon YS. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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