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DOKTORI ISKOLA

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ERDÉLYI TAMÁS

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Programvezető: Dr. Müller Veronika, egyetemi tanár

Témavezető: Dr. Müller Veronika, egyetemi tanár

CHARACTERIZATION OF INHALATION MANEUVERS AND PULMONARY DRUG DEPOSITION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

PhD thesis

TAMÁS ERDÉLYI, MD

Károly Rácz Doctoral School of Clinical Medicine

Semmelweis University

Supervisor:	Veronika Müller, MD, D.Sc
Official reviewers:	Zoltán Balikó, MD, Ph.D Zoltán Zádori, MD, Ph.D
Head of the Complex Examination Committee:	Romána Zelkó, D.Sc
Members of the Complex Examination Committee:	Dóra Krikovszky, MD, Ph.D Zoltán Horváth, Ph.D

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LIST OF ABBREVIATIONS

AE	Acute exacerbation
BMI	Body Mass Index
BTPS	Body temperature, pressure, water vapor saturated
CAT	COPD Assessment Test
CFC	Chlorofluorocarbon
COPD	Chronic obstructive pulmonary disease
CR	Coefficient of repeatability
DL_{CO}	Diffusion capacity of the lungs for carbon monoxide
DPI	Dry powder inhaler
ETD	Extrathoracic deposition
FDC	Fixed dose combination
FDTC	Fixed dose triple combination
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFA	Hydrofluroalkane
ICS	Inhaled corticosteroid
IVC	Inspiratory vital capacity
IVC_d	Through-device inspiratory vital capacity
LABA	Long-acting beta2-agonist
LAMA	Long-acting muscarinic antagonist
LF	Lung function
MABA	Muscarinic antagonist-beta2-agonist
MMAD	Mass median aerodynamic diameter
mMRC	Modified Medical Research Council
PD	Pulmonary deposition
PEF	Peak expiratory flow
PIF	Peak inspiratory flow
PIF_d	Through-device peak inspiratory flow

PI3Kδ	Phosphoinositide 3-kinase δ
pMDI	Pressurized metered dose inhaler
QoL	Quality of life
RV	Residual volume
SABA	Short-acting beta2-agonist
SAMA	Short-acting muscarinic antagonist
SEM	Standard error of the mean
SMI	Soft mist inhaler
SmPC	Summary of product characteristics
t_{bh}	Breath-hold time
t_{in}	Inhalation time
TLC	Total lung capacity
ULABA	Ultralong-acting beta2-agonist
V/Q	Ventilation/perfusion ratio
VAS	Visual Analogue Scale

1. INTRODUCTION

Aerosols play a leading role in our respiratory system. Bacterial, viral and fungal infections can enter our body through the airways but it is also an advantageous opportunity for therapeutic approaches. Different drugs, such as bronchodilators, corticosteroids and antibiotics can be administered via inhalation. Increasing effectiveness by local absorption and reducing systemic side effects make inhalation therapy a significant cornerstone of treating airway diseases. Chronic obstructive pulmonary disease (COPD) and asthma bronchiale affect over 0.5 billion patients worldwide and due to tobacco smoking and air pollution COPD prevalence tends to be higher and make COPD the third leading cause of death.(1-3) Regarding its growing prevalence, COPD patients need better therapeutic possibilities to improve pulmonary function and decrease mortality rates. COPD maintenance therapy contains three main groups of inhalative agents such as beta-adrenergic-agonists, muscarinic antagonists and corticosteroids.(2)

1.1. Chronic obstructive pulmonary disease (COPD)

1.1.1. Epidemiology and pathophysiology of COPD

COPD affects more than 380 million people worldwide.(4) The most important risk factor and the most frequent cause of COPD is tobacco smoking but several additional risk factors should be mentioned as dust, indoor air pollution from burning biomass fuels, noxious fumes and, moreover, individual genetical factors, effect of preterm birth, prenatal maternal smoke exposure and childhood infections.(5-8) The above mentioned factors result in pathological changes involving the airways, the parenchyma and even the vasculature. As a result of oxidative stress, increased macrophage cell count in the affected loci and elevation of inflammatory mediators, chronic inflammation develops in the wall of airways leading to airway wall thickening, airway narrowing, increased mucus production, smooth muscle remodeling, decreased mucociliary clearance on the long-term.(9-11) The symptoms of the disease are the consequences of the different

pathological changes, and include chronic cough, sputum production and shortness of breath, initially under exercise but later also at rest. These changes can lead to decrease in quality of life (QoL) and to an increased risk of infections resulting sudden worsening of symptoms – called acute exacerbations (AE).(2, 12) During stable condition or AEs inhaled agents like anti-inflammatory and bronchodilator drugs are the basis of therapy.(2)

1.1.2. Symptoms of COPD

Main symptoms of chronic obstructive pulmonary disease include dyspnea, chronic cough and chronic sputum production.(2) In cases with history of smoking or occupational exposure to fumes or dusts, clinician should consider COPD a potential underlying cause of varying symptoms.(8, 13) However, COPD patients experience signs of disease progression which are not specific for this disorder, several conditions might help the diagnosis. Usually, the first symptoms occur in middle age or elderly patients and most of them suffer only from effort dyspnea or recognize recurring infections, especially during cold weather episodes. Most patients realize problems when they are not able to perform different activities in the way as other persons in the same age while early diagnosis of COPD should be emphasized.(14) Despite the improvement of COPD diagnosis, many patients are misdiagnosed for asthma.(15) Regarding dyspnea, a useful assessment tool is the questionnaire for dyspnea by British Medical Research Council (mMRC).(16)

Hyperinflation caused by airway obstruction may result in hyperventilation as the elevated residual volume (RV) and its ratio to total lung capacity (TLC) cause decreased tidal volume.(17, 18) A brief but historical categorization of phenotypes might simplify identifying COPD patients, since a typical hyperinflated, emphysematous chest coupled with cachectic figure can be labeled as a “pink puffer”, while a “blue bloater” patient is usually overweight and tends to be cyanotic due to insufficient ventilation/perfusion ratio (V/Q) according to the traditional depiction by Netter.(19) Nonetheless, these categories are normally not completely distinguished and occur as a fusion of them, it supports the suspicion of COPD. The modern conception of COPD phenotypes separate the followings according its clinical representation: frequent exacerbators/chronic systemic

inflammation; chronic bronchitis; COPD-asthma overlap phenotype; emphysema/hyperinflation; chronic bacterial colonization.(20) However, there are no sharp boundaries between these phenotypes.

Physical changes resulting from COPD, especially hyperinflation causes lowered breathing and heart sounds which is roughly objective signs of the disease, however expirational wheezing refer to airway obstruction as well as prolonged forced expiration (> 6 seconds).(20) Additional symptoms as increased mucus production and chronic cough – even unproductive – may stand for COPD.(20) These symptoms support the diagnosis of COPD but further examinations are needed to establish the disease.

1.1.3. Diagnosis of COPD

The main diagnostic criteria of COPD are determined by lung function (LF) measurements. Dynamic parameters of expiration as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and their ratio (FEV1/FVC) describe the most appropriate yet clear way the worsening of breathing capacity in COPD. Certain numerical criteria of the diagnosis might lead to underdiagnosis of the disease under 50 years and overdiagnosis in elderly patients as LF parameters decrease by aging,(21, 22) however, because of its simplicity, the criterion of post-bronchodilator FEV1/FVC value less than 0.7 is widely used and serves as a cornerstone in international recommendations.(2) Reversibility test performed with definite amount of inhaled bronchodilator agents are inevitable to differentiate reversible and irreversible obstructive ventilatory disorders and must be carried out in the diagnostic process of COPD. Airway obstruction can be categorized by FEV1 decrease as shown in Table 1.(23) Besides FEV1, peak expiratory flow (PEF) might refer to airway obstruction and simpler to perform, though its sensitivity compared with FEV1 is moderate.(24) Body plethysmography tests present increasing values regarding RV, TLC and RV/TLC as described previously, while diffusion measurements may show decreased diffusion capacity of the lungs for carbon monoxide (DL_{CO}) in combined syndrome of emphysema and pulmonary fibrosis.(25)

Table 1. Grades and severity of airway obstruction in COPD patients according to GOLD 2023 Report.(26)

GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4	Very severe	FEV1 < 30% predicted

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

It is important to note that the classification of the disease is based not only on quantifiable changes in breathing capacity but also on the patients' QoL. Quality of life is assessed by two questionnaires according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), one of them was already mentioned before (mMRC) while the other is the COPD Assessment Test (CAT®) asking about eight different fields of limitation due the disease.(16, 27) Both of them representing an impaired QoL as their values increase. Besides QoL questionnaires, exacerbations mean a factor of deterioration of COPD. Categories of the disease according to the GOLD 2015 Report are presented in Table 2.(23) It is important to note that the latest categorization of COPD in 2023 places patients with more severe exacerbation history into one group as presented in Table 3.(26)

Table 2. Categories of COPD patients according to GOLD 2015 Report.(23)

Exacerbation history		
≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**C**	**D**
0 or 1 moderate exacerbations (not leading to hospitalization)	**A**	**B**
	mMRC 0-1 CAT < 10	mMRC 2-4 CAT ≥ 10
	Symptom assessment	

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: Modified Medical Research Council.

Table 3. Categories of COPD patients according to GOLD 2023 Report.(26)

<table>
<tr><td colspan="3">Exacerbation history</td></tr>
<tr><td>≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization</td><td colspan="2">E</td></tr>
<tr><td rowspan="3">0 or 1 moderate exacerbations (not leading to hospitalization)</td><td>A</td><td>B</td></tr>
<tr><td>mMRC 0-1
CAT < 10</td><td>mMRC 2-4
CAT ≥ 10</td></tr>
<tr><td colspan="2">Symptom assessment</td></tr>
</table>

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: Modified Medical Research Council.

1.1.4. Management of COPD

Treatment of COPD should be divided into two main groups, stable and exacerbated patients. Stable COPD patients use an inhalative regimen of combined bronchodilator agents, supplemented with inhaled corticosteroids (ICS). The recommended group of agents are shown in Table 4.(23) ICS are frequently debated agents in the treatment of COPD as several studies found increased risk of pneumonia using such drugs.(28-30) During an AE requiring hospitalization therapeutic scheme is usually complemented by systemic steroid, nasal oxygen supplementation and mucolytics while in severe cases phosphodiesterase inhibitors can be added.

Table 4. Therapeutic recommendations of inhaled medications in COPD according to GOLD 2015 Report.(23)

Category	Recommended inhaled medication
A	SABA* or SAMA*
B	LABA or LAMA
C	ICS + LABA or LAMA
D	ICS + LABA and/or LAMA

*When necessary; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta2-agonist; SAMA: short-acting muscarinic antagonist.

1.2. Inhalative agents

Inhalation therapy was known 4000 years ago in Egypt where Datura Stramonium leaves were burnt and its smoke containing scopolamin and atropin was inhaled, which agents had hallucinogenic effects and as anticholinergic drugs, functioned as bronchodilators.(31) Besides well-known bronchodilator and anti-inflammatory drugs many groups of different agents might be conveyed via our respiratory system for example antibiotics and novel inhaled medications as monoclonal antibodies, muscarinic antagonist-beta2-agonists (MABAs), inhalative phosphodiesterase-3/4 inhibitors, phosphoinositide 3-kinase δ (PI3Kδ) inhibitors, inhaled vaccines etc.(32-36)

Although, COPD patients might reach further therapeutic choices in the future, currently the international recommendations focus on the three main groups of beta-adrenergic-agonists, muscarinic antagonists and corticosteroids. Table 5 contains the currently available acting agents, combinations, compact inhaler types and duration of action according to GOLD 2023 Report.(26)

Table 5. Commonly used maintenance medications in COPD according to GOLD 2023 Report.(26)

Generic Drug Name	Inhaler Type	Duration of Action
ß-adrenergic agonists		
Short-acting (SABA)		
Fenoterol	pMDI	4-6 hours
Levalbuterol	pMDI	6-8 hours
Salbutamol (albuterol)	pMDI, MDI	4-6 hours
Terbutaline	DPI	4-6 hours
Long-acting (LABA)		
Formoterol	DPI	12 hours
Indacaterol	DPI	24 hours
Olodaterol	SMI	24 hours
Salmeterol	pMDI, DPI	12 hours
Muscarinic antagonists		
Short-acting (SAMA)		
Aclidinium bromide	pMDI	6-8 hours
Oxitropium bromide	pMDI	7-9 hours
Long-acting (LABA)		
Aclidinium bromide	pMDI, DPI	12 hours
Glycopyrronium bromide	DPI	12-24 hours
Tiotropium	pMDI, DPI, SMI	24 hours
Umeclidinium	DPI	24 hours
Combination of SABA+SAMA in one device		
Fenoterol/ipratoprium	SMI	6-8 hours
Salbutamol/ipratropium	SMI, pMDI	6-8 hours
Combination of LABA+LAMA in one device		
Formoterol/aclidinium	DPI	12 hours
Formoterol/glycopyrronium	pMDI	12 hours
Indacaterol/glycopyrronium	DPI	12-24 hours
Vilanterol/umeclidinium	DPI	24 hours
Olodaterol/tiotropium	SMI	24 hours
Combination of LABA+ICS in one device		
Formoterol/beclometasone	pMDI, DPI	12 hours
Formoterol/budesonide	pMDI, DPI	12 hours
Formoterol/mometasone	pMDI	12 hours
Salmeterol/fluticasone proprionate	pMDI, DPI	12 hours
Vilanterol/fluticasone furoate	DPI	24 hours
Triple Combination of LABA+LAMA+ICS in one device		
Fluticasone/umeclidinium/vilanterol	DPI	24 hours
Beclometasone/formoterol/glycopyrronium	pMDI, DPI	12 hours
Budesonide/formoterol/glycopyrrolate	MDI	12 hours

DPI: dry powder inhaler; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonists; LAMA: long-acting muscarinic antagonists; pMDI: pressurized metered dose inhaler; SABA: short-acting beta2-agonists; SAMA: short-acting muscarinic antagonists; SMI: soft mist inhaler.

1.2.1. Beta-adrenergic-agonists

Beta2-agonist have an effect on airway wall smooth muscle cells and by stimulating beta2-adrenergic receptors these drugs increase the cyclic adenosine-monophospate resulting in a functional antagonism of bronchoconstriction.(37) We differentiate subgroups by their duration of action and divide beta2-agonist in two main groups – short-acting beta2-agonists (SABAs) and long-acting beta2-agonists (LABAs). In the management of obstructive airway diseases SABAs and LABAs play a crucial role. However, for asthmatic patients LABAs alone are not permitted, only combination therapy is recommended according to the guidelines.(1, 38, 39) In the context of COPD, LABAs are the cornerstone of inhalative therapy, combined with muscarinic antagonists. SABA has a duration of acting of 4 to 6 hours.(40) These agents are mostly administered as reliever therapy in both COPD and asthma or used during disease worsening requiring hospitalization. LABAs have mostly 12 hours as duration of action but novel agents such as olodaterol or vilanterol act as ultralong-acting beta2-agonists (ULABAs) with a 24-hour-long duration of action, consequently given once daily.(40) While beta2-agonists have an impact on symptom improvement (41), do not modify the annual decrease of FEV1.(42)

1.2.2. Muscarinic antagonists

Muscarinic antagonists inhibit the effect of acetylcholine on M3 receptors and this inhibition results in blocking of bronchoconstriction and decrease in mucus production.(43,44) Short-acting muscarinic antagonists (SAMAs) also have an inhibitory effect on natural inhibitory M2 receptor, causing vagal bronchoconstriction.(45) Long-acting muscarinic antagonists (LAMAs) bind not so strongly to M2 receptors as SAMAs and have longer – 12 to 24 hours – duration of action, while SAMAs have 4 to 6 hours'

duration of action.(46-48) Muscarinic antagonists are essential in the treatment of COPD patients alongside with beta2-agonists. Some studies showed an improvement of symptoms in COPD in patients using muscarinic antagonists and a decrease in exacerbation rates but not direct increase in FEV1 compared to beta2-agonists.(49, 50) LAMAs also have a direct effect on improving airway ciliary function enhancing mucociliary clearance in COPD patients.(51) The use of these agents are relatively safe as adverse effects are unusual and the most frequently occurring is dryness of mouth as an anticholinergic effect.(44) By occasional cases, COPD patients treated by aerosols containing muscarinic antagonists, acute glaucoma was observed as the solution of muscarinic antagonists contacted the eyes.(52)

1.2.3. Inhaled corticosteroids

Inhaled corticosteroids have anti-inflammatory effect in airway diseases.(53) Nevertheless, airway inflammation in COPD is deemed to be unresponsive to inhaled corticosteroids, likely due to smoking.(54, 55) Unlike in asthma, in the therapy of COPD ICS is not considered as a monotherapy but combined with a LABA (ICS-LABA) or added to a LABA-LAMA combination to form an open triple therapy or be part of a fixed dose triple combination (FDTC) of ICS-LABA-LAMA.(2) In COPD, ICS was already investigated in many clinical studies to find out its therapeutical benefit and showed that ICS improves the exacerbation rate, LF and symptoms in combination with LABA versus mono-LABA and expresses the same advantage in a triple combination versus LABA-LAMA, or even ICS-LABA combination.(56-58) The side effects of corticosteroids are well-known, such as osteoporosis, hyperglycemia or increased risk of infections, however, inhalation route can reduce the disadvantageous impact of corticosteroids by local acting and the need for lower amount of ICS. Systemic adverse effects of ICS – such as adrenal suppression or skin thinning - are already documented but disputed as well.(59, 60) Oral candidiasis is a well-documented side effect but can be easily prevented by mouth rinse.(61) The association between increased risk of pneumonia ICS usage remains a subject of debate. While cases of pneumonia have been recorded during ICS usage, development of lower respiratory infections is influenced by numerous factors. In

situations where individuals encounter frequent exacerbations, ICS is recommended.(2, 57, 60, 62)

1.3. Types of inhalers

Inhalers are particular devices whose mechanisms and inner structure are constructed to form a mixture of inhalative drugs, carrier molecules and air which the patient can easily inhale in order to reach a satisfying deposition at the desired locations. Inhaler devices are designed to provide inhaled particles between one and five micrometers which are in the best size range to deposit in small airways where targets of COPD therapeutical agents take place.(63, 64) Three different forms of inhaled particles are available in clinical practice: solutions, suspensions and dry powders. These medications are conveyed by various types of inhalation devices divided into four main groups. One group is applied in emergency situations or serious cases where the patient's ability to inhale is limited.(65) This inhaler is the nebulizer which mostly requires electricity to function and regular maintenance.(66) The other three groups are compact, portable devices such as the pressurized metered dose inhalers (pMDIs), the dry powder inhalers (DPIs) and the soft mist inhaler (SMI).(64) Inhalation therapy of COPD is based on the use of the last three groups and the clinician has several options to choose with the purpose of an individualized and effective treatment.(2)

1.3.1. Pressurized metered dose inhalers

The pMDIs were the first compact inhaler devices. Initially, it was designed to administer epinephrine in asthma patients (Medihaler-Epi, 1956).(67, 68) Later on, the device took place in the maintenance treatment of obstructive ventilatory disorders and are available in many countries containing different combinations of SAMAs and SABAs, or LAMAs, LABAs and ICSs.(2) The main components of pMDIs are the canister containing the acting agents in liquid phases - solution or suspension – and the propellant, and the actuator.(69) The propellants were originally chlorofluorocarbons (CFCs) but since 1996 when the Montreal Protocol was implemented, the use of CFC is forbidden due to its damage to the ozone layer. After the prohibition of CFC hydrofluoroalkenes (HFAs) have

been applied as an alternative propellant. HFAs have been proved to be more suitable in this context, as they produce slower aerosol sprays than CFCs. This slower speed helps reduce the possibility of impaction in the laryngo-pharyngeal region before entering the airways.(70, 71) After the actuation of the device, a relatively fast spray is formed, which the patient can inhale with the right coordination. PMDIs have comparatively high deposition values (20-40% of the metered dose), but the main disadvantage of this particular type of inhalator device is that it is difficult to actuate and inhale at the same time.(72-74) When used correctly, pMDIs offer a widely available option in inhaled therapy containing numerous combinations of different inhalative medications.

1.3.2. Dry powder inhalers

DPIs are the most versatile inhaler devices nowadays. The first device was on the market from 1967 (Spinhaler) which was a single dose capsule inhaler.(68) Currently both single dose capsule inhalers and multi dose DPIs are available. The main difference using a DPI compared to a pMDI is that the former does not contain any propellant so that the patient has to generate a sufficient flow to remove the agents from its inner structure.(64, 75) The formulation of inhalative agents differs from pMDIs' as well. Instead of solution or suspension, DPIs contain a mixture of acting agents attached to carrier particles creating a distribution of inhalative agents developed by various pharmacological methods.(76) One notable advantage of DPIs is that the inhalation maneuver is independent from the act of loading the device, which reduces the influence of poor coordination on the efficiency of usage due to a lesser extent. In contrast to pMDIs, the size of inhaled agents is not constant but depends on the peak inspiratory flow (PIF) or, according to the latest studies, the pressure drop generated by the patient.(77, 78) The more powerful inhalation the patient produces, the more advantageous distribution of inhaled particles is the result as increased fine particle fraction contributes to better lung deposition.(79) Considering the above-mentioned factor, the use of some DPIs is limited in case of patients with impaired LF.(80)

1.3.3. Soft mist inhaler

SMI is the latest type of compact inhalers and is able to generate a slow running mist of fine particles. The only available device is called Respimat®, developed in 2004 by Boehringer Ingelheim.(68, 81) Similarly to pMDIs, it has a canister containing the active agents in a solution.(81) By actuating the device, a previously tensioned spring provides the energy to force a metered amount of medication through a special nozzle generating an aerosol of fine mists.(81) Compared to pMDIs, which create a relatively fast-moving aerosol increasing the number of impacted particles in upper airways, SMI forms a slow vapor giving the patient enough time to inhale and simultaneously lowering the rate of impaction.(82, 83) Due to its longer duration, the vapor provides better circumstances to reach a good coordination of actuation and inhalation resulting a theoretically better effectivity of deposition. The fraction of fine particles is approximately 75%, which is double the value of pMDIs. Respimat® has very low resistance(84), so patients with impaired LF parameters are able to use these devices. ICSs are currently not available in SMI.

1.3.4. Nebulizers

With the development of pMDIs, nebulizers also became a cornerstone of inhaled drug delivery, not only in obstructive pulmonary diseases but also in infections, as nebulizers are able to aerosolize many types of drugs such as antibiotics, mucolytics and bronchodilators. Three main categories of nebulizers are used: jet nebulizers, ultrasonic nebulizers and mesh nebulizers.(64) Jet nebulizers are the most widely used and these are mostly tabletop devices using a compressor to generate flow of compressed air between 2 and 10 L/min.(66) Compressed air draws medication through a capillary tube from a reservoir and with a nozzle the medication can be aerosolized. Most frequently, jet nebulizers are applied with a corrugated tube as a reservoir, however, the flow and aerosol forming is constant in most cases so the loss of medication during breath-hold and exhalation is significant. Newly developed devices like breath-enhanced and breath-actuated jet nebulizers are dedicated to decrease the wastage of medication and also the exposure the health-care personnel.(66) Despite its lower efficacy, jet nebulizers are still cheaper, easy to use and are able to generate aerosols from viscous fluids and

suspensions.(66) Ultrasonic nebulizers include a piezoelectric crystal vibrating at high frequencies to generate aerosol.(85) Ultrasonic nebulizers have some disadvantages compared to jet nebulizers since they are not able to aerosolize viscous fluids and might degrade heat-sensitive-materials.(66) The last group of nebulizers are the mesh nebulizers which devices use also piezoelectric crystals in a form of a mesh or an aperture plate.(86) It has many advantages compared to ultrasonic nebulizers such as smaller residual volume and higher fine particle fraction. Owing to the latter, mesh nebulizers can be 2 or 3 times more effective regarding pulmonary deposition (PD), compared to jet nebulizers.(87) Delivery of viscous fluids are still an unsolved problem by mesh nebulizers as it can clog the plate during operation but mesh nebulizers can easily deliver solutions and suspensions.(66, 88)

1.4. Pulmonary deposition

Respiratory system provides a very efficient way for medications to be administered in several conditions. As the same amount of blood flows through the lungs as the other organs and tissues of our body, our respiratory system has the best blood supply of our circulation making it an appropriate locus to deliver therapeutical agents.(89) Regarding systemic therapies, lungs give a good opportunity for fast absorption and to increase a particular agent's serum concentration as it avoids first pass metabolism but its measurement possibilities create an obstacle in achieving effective therapy.(90) Although, administering systemic therapy via inhalation is easy and noninvasive, its unreliability makes it subordinate against intravenous drug administration.

The outstanding role of inhalative medication prevails in medical conditions where the target of treatment is located in the airways.(91) Proper deposition depends on the type of medication – ICS might act beneficially throughout the whole conductive airway region as an anti-inflammatory agent, meanwhile muscarinic antagonists and bronchodilators must deposit in loci where mucus production and smooth muscles are substantial.(91) Inhalative medications dispose different pharmacological characteristics such as formulation and size distribution. Inhaled aerosols consist medication in liquid or solid particles dispersed in air. Regardless its liquid or solid phase, the size of particle determinates its locus of deposition.(91) There are three major mechanisms of deposition:

impaction, sedimentation and diffusion.(92) Inertial impaction is the most considerable before entering lower respiratory system, in the pharyngeal and laryngeal region and the main bronchi.(92) Usually, impaction affects particles larger than 10 μm but above 5 μm is still significant.(92) Gravitational sedimentation is the main mechanism for inhaled particles to deposit in the small airways, the range of particle size is between 1 and 8 μm.(92) Brownian diffusion plays role in the deposition of particles under 0,5 μm.(92) Normally, during a 5 or 10-second-long breath-hold time during drug inhalation, a significant fraction of small particles do not settle and are basically exhaled. Generally, aerosols are not monodisperse systems where all particles are at the same size but polydisperse systems with a quite extensive range of particles. By determining a particle's impact, not its size but its mass is taken into account as a 10 μm particle contains the same acting capacity as 1,000 particles with the diameter of 1 μm. Mass median aerodynamic diameter (MMAD) can describe an aerosol meaning that half of the particles are smaller while the other half of the particles are larger than the certain value.(93) Gravitational sedimentation is the most meaningful way of deposition in inhalative treatment of COPD, however, targeting this particular area of small airways are influenced not only by formulation and size distribution but the amount of acting agents and LF parameters of the patient like inspiratory vital capacity (IVC), time of inhalation and breath-hold and - in case of DPIs – the PIF.(94) In summary, the ideal inhalation therapy delivers particles between 1 and 5 μm in order to reach a high deposition in small airways and peripheral lung regions. As the inhaled agents must act locally in order to increase its therapeutical effect and decrease its side effects, we have inspected the effectivity of pulmonary drug delivery and quantified the deposited amount in comparison with the metered dose.

1.4.1. Measurement of pulmonary drug delivery

Measuring pulmonary drug delivery challenges investigators. *In vivo* studies are mainly examinations using radioscintigraphy.(95, 96) Radioscintigraphy is a well-known method to evaluate pharmacokinetic and pharmacodynamic characteristics of different drugs in the human body. Besides the gastrointestinal tract, our respiratory system might be easily examined with radiolabeled particles. Several methods are applicable in order to radiolabel inhaled particles in different formulations.(97) For example, drugs dissolved

in solutions are usually labeled with ^{99m}Tc-DTPA, where after absorbing particles through healthy lungs, the technetium-labeled molecule has a half-time approximately 1 hour in the body, as it is excreted from the blood throughout the kidneys.(95) Particles not entering the respiratory system then swallowed are not absorbed in the gastrointestinal tract helping the separation of different fractions of the emitted dose. Various drugs can be radiolabeled and then inhaled after generating aerosols via nebulizers, pMDIs and DPIs.(97) However, there is a major ethical concern regarding radioscintigraphy as it might expose radiation burden on patients or healthy volunteers. Radiolabeled inhaled particles may not present higher risk for the human body as other novel medications, however all studies must be accepted by the standards set by Ethical Committees. In addition to *in vivo* techniques, certain studies have employed pharmacokinetic methods to assess the pulmonary deposition of inhaled particles by measuring levels of specific agents in the bloodstream and their urinary excretion.(98-100) However, it is important to note that pharmacokinetic methods cannot differentiate between the deposition in certain regions of the lungs and cannot reveal the amount of drug eliminated through mucociliary clearance.(101) *In vitro* studies are based on replicas of the human respiratory system. *In vitro* drug delivery evaluation setup performed by Delvadia et al. contained an inhaler attached to a replica of the upper airways which was applied as a small, medium and large model representing anatomical differences.(102) The copy of the lower airways was positioned in a chamber modeling the human chest and further connected to a breathing apparatus separated by a filter.(102) Throughout this system the deposition of inhaled drugs could be measured by high-performance liquid chromatography.(102) In vitro studies are advantageous considering that patients or healthy volunteers are not required to perform even several evaluations yet this technique has limitations regarding the lack of anatomical variabilities of the models and must be validated by *in vivo* studies. *In silico* methods provide an alternative where numerical modeling or computational fluid dynamics are able to perform thousands of drug delivery evaluations without the presence of patients or healthy volunteers.(103-105) In silico measurements need data about anatomical structures of the respiratory system, LF parameters such as static and dynamic values and information about the inhaled particles and its size distribution.(105-107) By validating these methods by *in vivo* studies, various evaluations can be carried out via *in silico* methods.(104, 107) The Stochastic Lung Model was developed in 1990 and based

on Monte Carlo technique.(105) The model is able to simulate the deposition probability of a particular inhaled particle in the airways using previously measured geometric data and LF values differentiating extrathoracic, bronchial and acinar deposition.(105)

2. OBJECTIVES

1. Comparing LF parameters measured by a hand-held spirometer using four different commercially available inhaler devices in stable and exacerbated COPD patients and healthy subjects.
2. Investigating repeatability of inhalation maneuvers using four different commercially available inhalation devices.
3. Calculating pulmonary and extrathoracic deposition based on inhalation maneuvers performed using three commercially available low-resistance inhaler devices.
4. Investigating repeatability of pulmonary and extrathoracic deposition in three commercially available inhaler devices.

3. METHODS

3.1. Subjects

Patients with stable and exacerbated COPD as well as healthy volunteers were recruited to participate in our study which involved two main phases. In the first phase (Phase 1), stable (LF-COPD-S, n=16) and exacerbated (LF-COPD-AE, n=15) COPD patients took part in our study alongside healthy volunteers (LF-Controls, n=22). All COPD patients were diagnosed according to GOLD as post-bronchodilator FEV1/FVC <0.7 by a respiratory specialist. Exacerbated patients were recruited <72 hours after hospital admission due to severe AE. All patients belonged to D category according to the then valid (2015) GOLD Guideline.(23) Therapy was chosen by the treating physician, but all patients were given systemic corticosteroid. Subjects with acute respiratory tract infections in stable COPD and control group were excluded, as were exacerbated patients with pneumonia or the need for non-invasive ventilation. Healthy volunteers were the employees of the Department of Pulmonology. Subject recruiting took place between April and December 2015 at the Department of Pulmonology, Semmelweis University, Budapest, Hungary. In the first phase, patients performed standard LF measurements, body plethysmography, inhalation maneuvers through commercially available inhalation devices, symptoms and QoL were assessed.

In the second phase (Phase 2), we formed groups of subjects for whom body plethysmography measurements were available and modeled PD with the Stochastic Lung Model. Numerical modeling was carried out in groups of stable (PD-COPD-S, n=13) and exacerbated (PD-COPD-AE, n=12) COPD patients and healthy volunteers (PD-Controls, n=17). Body plethysmography values were not available in cases where subject's compliance was insufficient.

All individuals were informed about the aims and methods of the study and signed the informed consent form. The study was approved by the ethics committee (TUKEB 239/2015).

3.2. Study design

Subjects performed LF and body plethysmography in a single visit. After a 30-minute-long break, through-device inhalation maneuvers were evaluated using at least three inhaler devices, followed by a second sequence of inhalation maneuvers through each inhaler device. Between the two different sequences, a 5-minute-long break took place. During the breaks we assessed symptoms and quality of life forms were filled. Repeatability of inhalation parameters were calculated between the two subsequent inhalations of each device.(108) PD was modeled later by the Stochastic Lung Model, independently from subject attendance.(109)

3.3. Lung function and body plethysmography measurements

Pulmonary function measurements were performed using an electronic spirometer and body plethysmography (PDD-301/s; Piston, Budapest, Hungary) according to the American Thoracic Society and European Respiratory Society guidelines.(110) LF variables were presented as the percentage of predicted values using references of the European Coal and Steel Community.(111, 112) None of the records was a post-bronchodilator measurement.(108, 109)

3.4. Inhalation maneuvers through different inhalers

Inhalation maneuvers were performed through four commercially available inhalers in our investigation: one pMDI by Chiesi® (Chiesi®-pMDI), two DPIs (Ellipta® and Genuair®) and one SMI (Respimat®). We did not apply inhalation devices with active agents. Subject performed inhalation maneuvers using an electronic spirometer (PDD-301/s; Piston, Budapest, Hungary) with built-in ambient temperature, pressure and humidity sensors for the fully automatic body temperature, pressure, water vapor saturated (BTPS) correction. Measurement apparatus included a PinkFlow flowmeter (PPF-18, Piston, Budapest, Hungary), determining flow based on the principle of a symmetric and averaging Pitot tube; a connecting piece which was a metal ring with an adaptable rubber cover preventing air leak between the inhaler and the PinkFlow, an inhaler device and a bacterial filter attached to the opposite side of the flowmeter through

which the subjects were asked to perform maneuvers. The measurement setup is depicted on Figure 1. Initially, eight different inhalers were tested with a 3-L calibration pump at 30-60-90 L/min flow to assess whether our equipment could correctly measure flow through different devices. Only four inhalers were able to fulfill the criteria to provide reliable measurement parameters. Before inhalation maneuvers, we instructed subjects about the recommended usage of each device provided by their manufacturers. Subjects were allowed to ask questions before the inhalations but were not allowed to practice them. Steps of the inhalation maneuver were as follows: (1) preparation of the device; (2) long exhalation; (3) attachment of the inhaler to the flexible connecting piece; (4) deep inhalation through the inhaler to total lung capacity, with optimal actuation of pMDI and SMI by the examiner and simultaneous recording of the prespecified parameters; (5) breath-holding for 10 seconds (when possible) while the inhaler device was detached from the connecting piece; and (6) long exhalation. Measured parameters were the following: through-device inspiratory vital capacity (IVC_d), through-device peak inspiratory flow (PIF_d), inhalation time (t_{in}) and breath-hold time (t_{bh}). Subjects performed the measurements through all four inhalers first in a random manner, then repeated the inhalation maneuvers in a different second sequence with at least a 5-minute-long break between sequences. Patients and controls carried out a total of six to eight recordings. Patients were taking inhaled medication, but the specific types of their regular inhalers were not recorded. On the other hand, the controls had no prior experience with inhalation devices prior to the study.(108, 109)

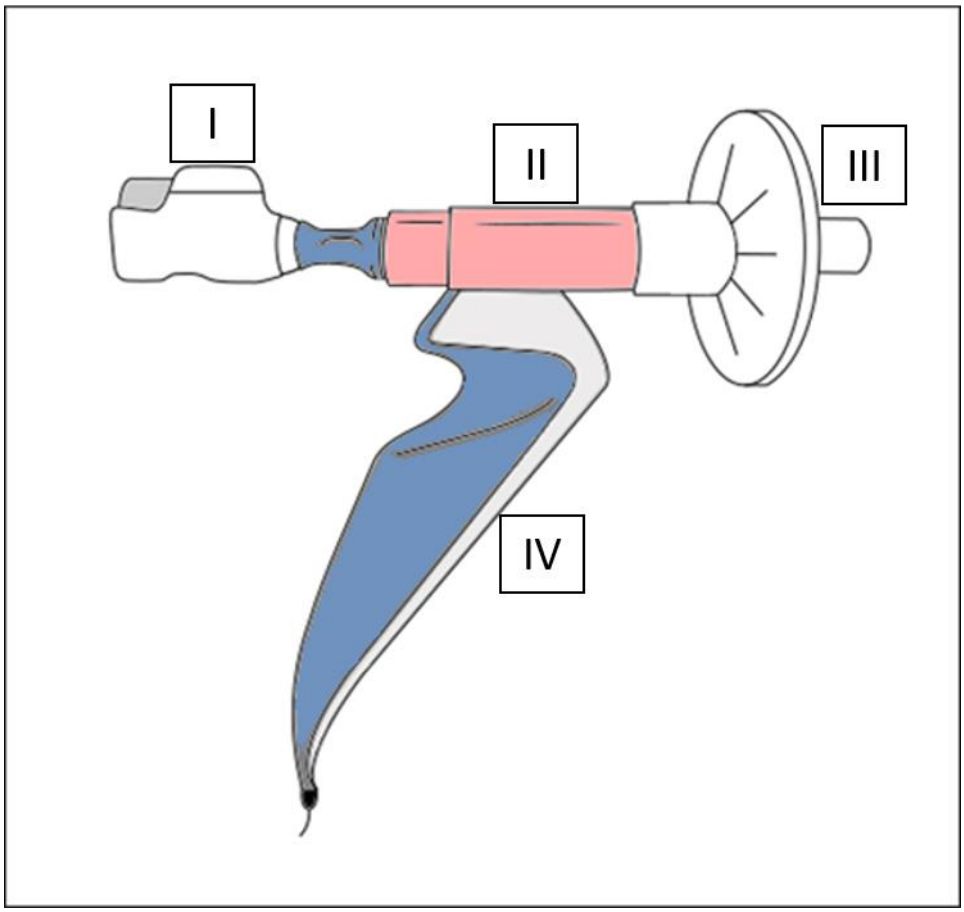

Figure 1. Measurement setup attached to Genuair®. I: Inhaler device, II: Flowmeter, III: Bacterial filter, IV: Spirometer. Another version of this figure has been published in Erdelyi et al.(108) Copyright © 2020 Mary Ann Liebert, Inc.

3.5. Assessment of symptoms and quality of life

As a part of the investigation, subjects were asked to fill out questionnaires which included the mMRC and the Hungarian version of CAT®. Additionally, participants used the visual analogue scale (VAS), scaled from 0 to 10, to assess the general health condition of the subjects. No health problem was represented by a score of 0, while a score of 10 suggested poor health condition.(108, 109)

3.6. Numerical modeling of pulmonary and extrathoracic deposition

Using the Stochastic Lung Model, we calculated deposition fraction values as PD and extrahoracic deposition (ETD). The calculated values were expressed as a percentage of the metered dose. The initial development of the model was carried out by Koblinger and Hofmann, and it has undergone subsequent development. The Stochastic Lung Model has been utilized to simulate the deposition of various aerosols, including inhaled drug particles, within the pulmonary and extrathoracic regions. The model's structure of the conducting airways is generated stochastically based on distribution functions for airway lengths, diameters, branching angles, and gravity angles (Raabe). The geometric representation of the acinar airways is derived from the Haefeli-Bleuer and Weibel description. Subsequently, deposition fractions in the extrathoracic airways are calculated using empirical deposition formulas. In the pulmonary airways, deposition fractions are modeled by tracking a large number of inhaled particles from inhalation until their deposition within the airways or their leave from the lungs through exhalation. Particle deposition can occur through impaction, gravitational sedimentation and Brownian diffusion. Input data such as breathing parameters, the size distribution and density of the drug particles of the drug particles are required. Standard spirometry and body plethysmography measurements are utilized to obtain inhalation parameters. RV and through-device spirometry data, such as IVC_d, t_{in} and t_{bh} were applied as input values, which were provided for both Chiesi®-pMDI and Respimat® devices. Genuair® was excluded from deposition calculations due to missing data. For the calculation we used the particle size distribution values of Spiriva® Respimat®, Foster® pMDI and Trimbow® pMDI. PD and ETD values were calculated from the first and second inhalation maneuver and their mean was used for further statistical analysis.(109)

3.7. Statistical analysis

Statistical analysis was performed using GraphPad Prism Software 8 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics V22 (International Business Machines Corporation, NY, USA). The results are expressed as the mean ± standard error of the mean (SEM) or median (interquartile range). One-way ANOVA followed by Bonferroni's multiple comparison test or Kruskal-Wallis test with Dunn's multiple

comparison test were used as appropriate. Repeatability of deposition values was assessed by the Bland-Altman test. Results were considered to be statistically significant when the p value was less than 0.05.(108, 109)

4. RESULTS

4.1. Phase 1

4.1.1. Clinical characteristics of participants

The summary of the characteristics of patient groups and control volunteers is provided in Table 6. There were significant differences between COPD patients and the control group in terms of age, current smoking habits and cumulative smoking history. Patients with AE were considerably younger and had a higher proportion of current smokers, but had smoked fewer pack years compared to patients in the LF-COPD-S group. All patients in the LF-COPD-AE group were classified as GOLD D, indicating they required hospitalization due to a relapse and no previous stable state was available for them. COPD patients had a high prevalence of comorbidities, particularly vascular comorbidities in the LF-COPD-AE group. Patients with exacerbation presented more symptoms based on mMRC, CAT® and VAS scores. The maintenance inhalation therapy was similar among the patient groups, with the majority of patients receiving triple therapy.(108)

Table 6. Clinical characteristics of controls and patients in Phase 1.

	LF-Controls (n = 22)	LF-COPD-S (n = 16)	LF-COPD-AE (n = 15)
Female/male	14/8	10/6	11/4
Age (years)	44 ± 3	66 ± 2*	59 ± 2*
BMI (kg/m^2)	24.9 ± 0.8	25 ± 1.2	25.7 ± 1.8
Smoking habit, n (%)**			
Current smoker	11 (50)	5 (31.25)	10 (67)
Former smoker	1 (4.5)	8 (50)	5 (33)

Never smoker	10 (45.5)	3 (18.75)	0 (0)
Pack year	18 ± 4	50 ± 6*	36 ± 3*
GOLD category 2015, n (%)			
A	NA	2 (12.5)	0 (0)
B	NA	2 (12.5)	0 (0)
C	NA	5 (31)	0 (0)
D	NA	7 (44)	15 (100)
Quality of life			
mMRC	0 (0–0)[1]	2 (1–2)[2]*	4 (3–4)*
CAT®	3 (1–7)	9 (7–22)[2]*	26 (15–31)*
VAS	1 (0–3)[3]	5 (4–5)[2]*	7 (5–10)[4]*
Comorbidities, n (%)			
Osteoporosis		1 (6)	4 (7)
Diabetes mellitus		1 (6)	3 (2)
Hypertension		4 (25)	2 (13)
Atherosclerosis		0 (0)	5 (33)[#]
Myocardial infarct		0 (0)	2 (13)
Cerebral stroke		0 (0)	4 (27)[#]
Maintenance COPD therapy, n (%)			
ICS	NA	12 (75)	14 (93)
LABA	NA	15 (94)	15 (100)
LAMA	NA	15 (94)	15 (100)
Theophylline	NA	4 (25)	7 (47)

* $p < 0.05$ vs. Control, #$p < 0.05$ vs S-COPD. ** Chi-square test: $p < 0.01$. [1]n = 21; [2]n = 12; [3]n = 20; [4]n = 14. BMI: Body Mass Index; CAT: COPD Assessment Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting $beta_2$-agonist; LAMA: long-acting muscarinic antagonist; LF-COPD-AE: patients with exacerbated COPD; LF-COPD-S: patients with stable COPD; mMRC: modified Medical Research Council; NA: not applicable; VAS: Visual Analogue Scale. Another version of this table has been published in Erdelyi et al.(108)

4.1.2. Lung function results

COPD groups exhibited similarly severe airflow obstruction and lung hyperinflation based on LF parameters, whereas the LF-Controls group had normal LF parameters, as shown in Table 7.(108)

Table 7. Lung function values in Phase 1.

	LF-Controls (n = 22)	LF-COPD-S (n = 16)	LF-COPD-AE (n = 15)
FVC, % predicted	100 ± 3	75 ± 6*	63 ± 6*
FEV_1, % predicted	95 ± 2	39 ± 5*	32 ± 4*
FEV_1/FVC, %	80 ± 2	43 ± 3*	46 ± 3*
PEF, % predicted	84 ± 7	39 ± 4*	32 ± 2*
$FEF_{25-75\%}$, % predicted	78 ± 5	16 ± 3*	16 ± 2*
PIF, L/s	4.8 ± 0.4	2.5 ± 0.2*	2.5 ± 0.3*
IVC, % predicted	98 ± 2	70 ± 6*	64 ± 5*
TLC, % predicted	93 ± 2	104 ± 6	113 ± 8*
TGV, % predicted	119 ± 5	168 ± 12*	193 ± 15*
RV, % predicted	83 ± 6	152 ± 17*	192 ± 19*
RV/TLC	0.28 ± 0.02	0.56 ± 0.04*	0.66 ± 0.04*
Raw, % predicted	108 ± 6	295 ± 3*	297 ± 31 *

* $p < 0.05$ vs. Control. $FEF_{25-75\%}$, forced expiratory flow at 25-75% of the pulmonary volume; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; IVC, inspiratory vital capacity; LF-COPD-AE: patients with exacerbated COPD; LF-COPD-S: patients with stable COPD; PEF, peak expiratory flow; PIF, peak inspiratory flow; Raw, airway resistance; RV, residual volume; TGV, thoracic gas volume; TLC, total lung capacity. Another version of this table has been published in Erdelyi et al.(108)

4.1.3. Through-device inhalation parameters using different inhalers

The results of testing IVC_d, PIF_d, t_{in} and t_{bh} for all four devices are presented in Table 8. Among the controls, IVC_d was lower for all devices, whereas both COPD groups showed only a slight decrease. Notably, both LF-Controls and LF-COPD-AE had significantly lower PIF_d compared to PIF during spirometry for all devices. In the LF-COPD-S group, PIF_d was significantly reduced only during inhalation through Genuair®. There were no significant differences in IVC_d and PIF_d between COPD groups for each device. On average, t_{in} ranged from 2 to 3 seconds, except for Genuair® in LF-Controls and LF-COPD-AE patients. The mean t_{bh} exceeded 10 seconds in LF-Controls and LF-COPD-S, while it slightly fell below the target in LF-COPD-AE patients.(108)

Table 8. Spirometric and inhalation parameters measured through the different inhalers in Phase 1.

LF-Controls (n=22)				
Spirometry:	IVC (L)	3.90 ± 1.06		
Spirometry:	PIF (L/s)	4.80 ± 1.61		
	Ellipta®	Chiesi®-pMDI	Respimat®	Genuair®
IVC_d (L)	3.41 ± 0.78	3.30 ± 0.88	3.58 ± 0.85	3.21 ± 0.91
PIF_d (L/s)	1.70 ± 0.49*	2.43 ± 0.97*	2.02 ± 0.67*	1.11 ± 0.38*
t_{in} (s)	2.94 ± 1.05	2.47 ± 1.00	2.70 ± 1.11	4.21 ± 1.50
t_{bh} (s)	10.04 ± 0.72	9.96 ± 0.53	10.06 ± 0.78	10.21 ± 0.78
LF-COPD-S group (n=16)				
Spirometry:	IVC (L)	2.20 ± 0.85#		
Spirometry:	PIF (L/s)	2.50 ± 0.77#		
	Ellipta®	Chiesi®-pMDI	Respimat®	Genuair®

IVC_d (L)	2.06 ± 0.73	2.12 ± 0.68	2.18 ± 0.81	1.76 ± 0.59
PIF_d (L/s)	1.35 ± 0.52	1.80 ± 0.64	1.53 ± 0.60	0.92 ± 0.26*
t_{in} (s)	2.43 ± 0.89	2.36 ± 1.02	2.49 ± 1.02	2.88 ± 0.33#&
t_{bh} (s)	10.35 ± 0.64	10.32 ± 0.51	10.49 ± 0.75	10.24 ± 0.82
LF-COPD-AE group (n=15)				
Spirometry:	IVC (L)	2.12 ± 0.90#		
Spirometry:	PIF (L/s)	2.51 ± 1.15#		
	Ellipta®	Chiesi®-pMDI	Respimat®	Genuair®
IVC_d (L)	2.09 ± 0.98	2.00 ± 0.93	2.15 ± 0.94	1.99 ± 1.11
PIF_d (L/s)	1.17 ± 0.37*	1.68 ± 0.47*	1.39 ± 0.43*	0.78 ± 0.24*
t_{in} (s)	2.81 ± 0.99	2.31 ± 0.99	2.55 ± 0.96	3.46 ± 1.09
t_{bh} (s)	9.52 ± 0.95	9.67 ± 0.59	9.50 ± 1.35	9.88 ± 0.95

IVC: inspiratory vital capacity; PIF: peak inspiratory flow; IVC_d: through-device inspiratory vital capacity; LF-COPD-AE: patients with exacerbated COPD; LF-COPD-S: patients with stable COPD; PIF_d: through-device peak inspiratory flow; t_{in}: inhalation time; t_{bh}: breath hold time; *$p<0.05$ vs. values obtained by standard spirometry; #$p<0.05$ vs. Control group; &$p<0.05$ vs. LF-COPD-AE. Another version of this table has been published in Erdelyi et al.(108)

4.1.4. Repeatability of through-device inhalation parameters

To assess the variability of inhalation maneuver parameters across different devices, the Bland-Altman analysis was employed. Given the limited number of patients in both groups, data from COPD patients who underwent measurements with all devices (LF-COPD-S and LF-COPD-AE) were combined to form the All-LF-COPD group (n=20).

Significant differences were observed among the tested devices for both PIF_d and IVC_d (Figure 2 to Figure 5). In the figures, the X-axis represents the mean of the two measurements for IVC_d and PIF_d, while the Y-axis represents the difference between the first and second measurements.

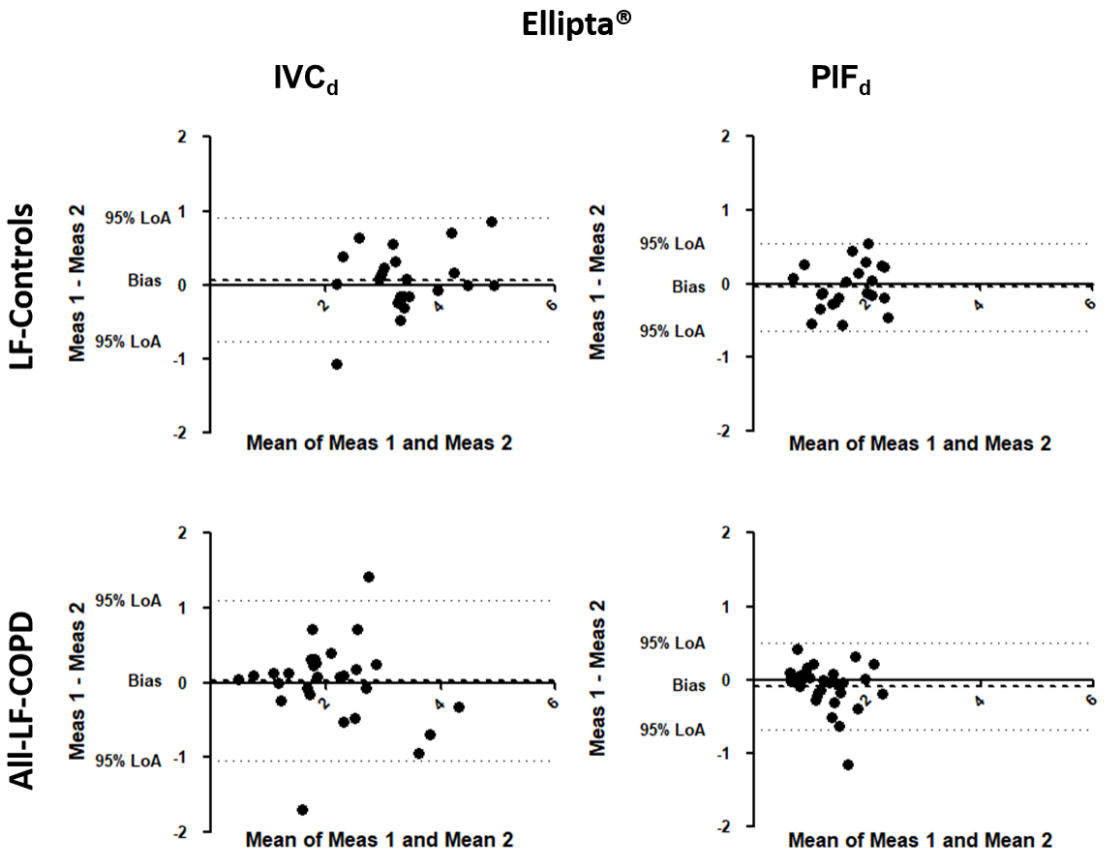

Figure 2. Bland-Altman analysis of through-device measurements for Ellipta®.
The X-axis represents the mean of the two measurements for IVC_d and PIF_d, while the Y-axis shows the difference of the repeated measurements (1st measurement–2nd measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects.
IVC_d: through-device inspiratory vital capacity; LoA: Bland-Altman 95% limits of agreement; Meas: measurement; PIF_d: through-device peak inspiratory flow. Another version of this figure has been published in Erdelyi et al.(108) Copyright © 2020 Mary Ann Liebert, Inc.

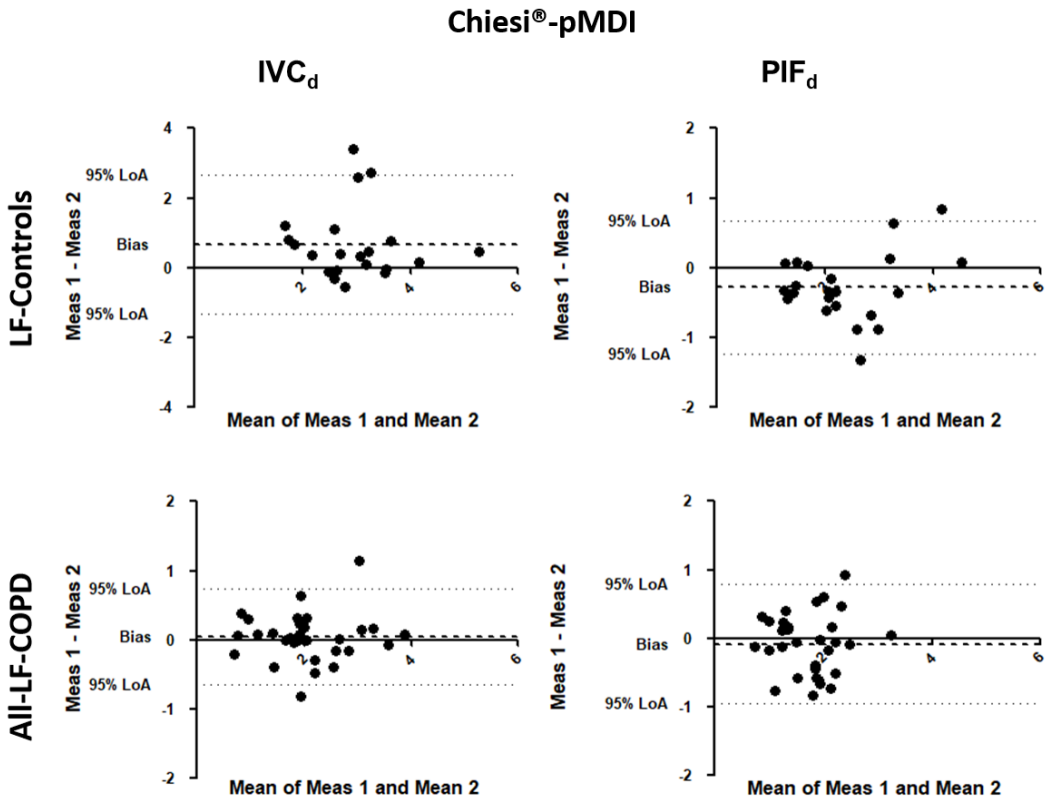

Figure 3. Bland-Altman analysis of through-device measurements for Chiesi®-pMDI. The X-axis represents the mean of the two measurements for IVC_d and PIF_d, while the Y-axis shows the difference of the repeated measurements (1st measurement–2nd measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects.

IVC_d: through-device inspiratory vital capacity; LoA: Bland-Altman 95% limits of agreement; Meas: measurement; PIF_d: through-device peak inspiratory flow. Another version of this figure has been published in Erdelyi et al.(108) Copyright © 2020 Mary Ann Liebert, Inc.

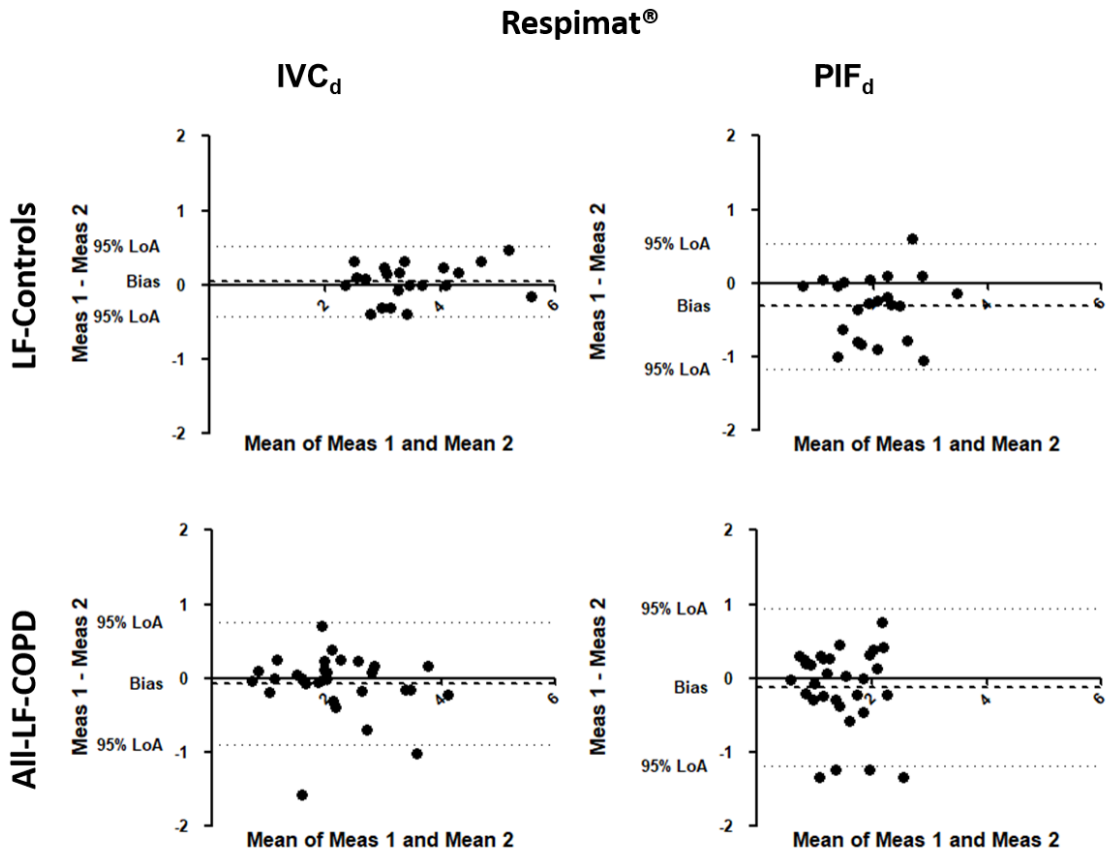

Figure 4. Bland-Altman analysis of through-device measurements for Respimat®. The X-axis represents the mean of the two measurements for IVC_d and PIF_d, while the Y-axis shows the difference of the repeated measurements (1st measurement–2nd measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects.

IVC_d: through-device inspiratory vital capacity; LoA: Bland-Altman 95% limits of agreement; Meas: measurement; PIF_d: through-device peak inspiratory flow. Another version of this figure has been published in Erdelyi et al.(108) Copyright © 2020 Mary Ann Liebert, Inc.

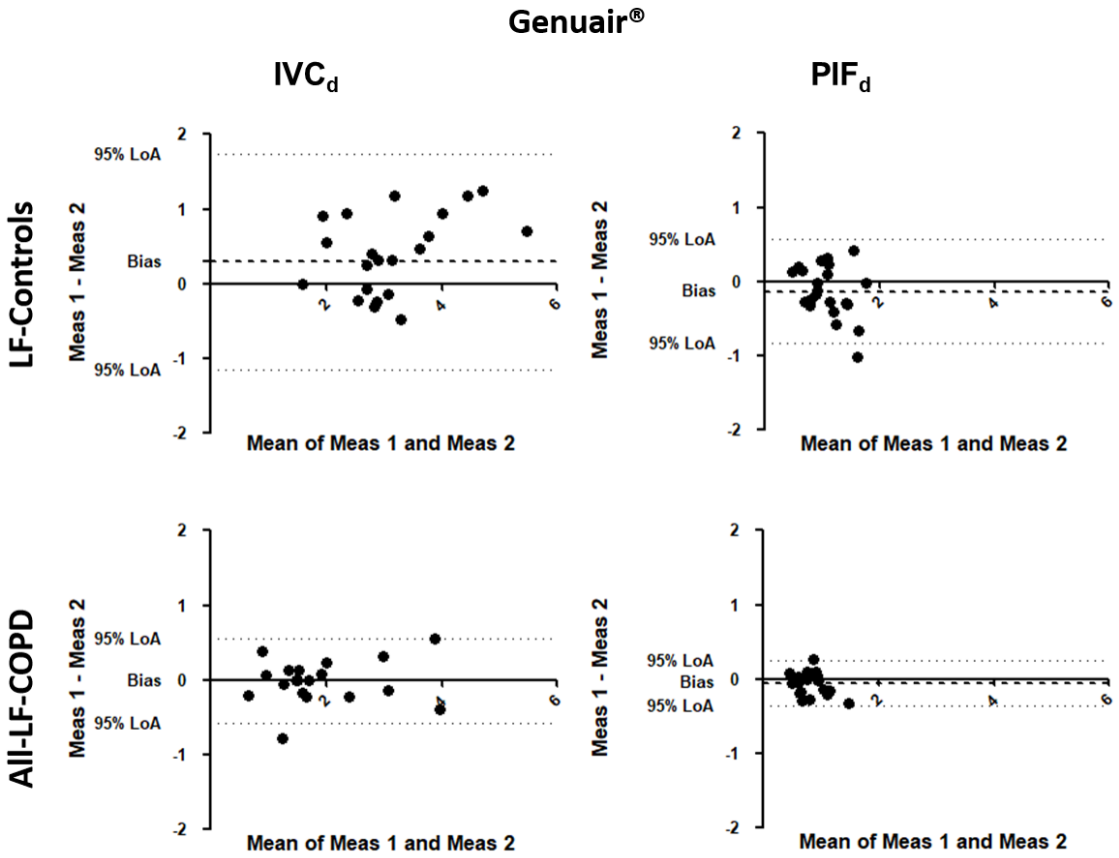

Figure 5. Bland-Altman analysis of through-device measurements for Genuair®.
The X-axis represents the mean of the two measurements for IVC_d and PIF_d, while the Y-axis shows the difference of the repeated measurements (1st measurement–2nd measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects.
IVC_d: through-device inspiratory vital capacity; LoA: Bland-Altman 95% limits of agreement; Meas: measurement; PIF_d: through-device peak inspiratory flow. Another version of this figure has been published in Erdelyi et al.(108) Copyright © 2020 Mary Ann Liebert, Inc.

In addition, we determined the bias, which represents the difference between the X-axis and the average mean of the two measurements for PIF_d and IVC_d in both LF-Controls and All-LF-COPD groups for each device. This analysis allowed us to assess the similarity of these parameters between the two measurements and their deviation from zero. The results are presented in Table 9 (one-sample t-test). We observed that in the

control groups, PIF_d was significantly higher during the second measurement when using Chiesi®-pMDI and Respimat® devices, and there was a trend towards higher values for the second maneuver with Genuair®. Additionally, we noticed a trend towards higher first IVC_d with Genuair® in the control group. Interestingly, in the patient group, there was only a tendency for higher PIF_d during the second measurement with Genuair®, but no significant bias in PIF_d or IVC_d was observed for any inhaler in COPD patients.(108)

Table 9. Repeatability of through-device inhalation parameters in Phase 1.

		LF-Controls group					All-LF-COPD group			
	n	**Bias**	**p-value***	**95% LoA**	**CR**	**n**	**Bias**	**p-value***	**95% LoA**	**CR**
IVC_d, L										
Ellipta®	22	0.068	0.47	-0.772–0.907	±0.831	30	0.026	0.80	-1.056–1.109	±1.066
Chiesi®-pMDI	22	0.049	0.44	-0.522–0.620	±0.566	31	0.048	0.46	-0.643–0.739	±0.686
Respimat®	22	0.040	0.45	-0.432– 0.511	±0.467	31	-0.075	0.33	-0.900–0.751	±0.828
Genuair®	22	0.294	0.08	-1.156–1.743	±1.528	20	0.014	0.83	-0.586–0.558	±0.558
PIF_d, L/s										
Ellipta®	22	-0.049	0.47	-0.651–0.554	±0.596	30	-0.095	0.10	-0.692–0.502	±0.616
Chiesi®-pMDI	22	-0.282	**0.01**	-1.235–0.671	±1.083	31	-0.085	0.30	-0.961–0.790	±0.877
Respimat®	22	-0.319	**0.002**	-1.170–0.532	±1.041	31	-0.128	0.20	-1.198–0.941	±1.082
Genuair®	22	-0.135	0.09	-0.833–0.564	±0.731	20	-0.063	0.09	-0.367–0.242	±0.321

CR: coefficient of repeatability; IVC_d: through-device inspiratory vital capacity; LoA: Bland-Altman 95% limits of agreement; N: number of subjects; PIF_d: through-device peak inspiratory flow *p-value for one-sample t-test of the bias. Another version of this table has been published in Erdelyi et al.(108)

The 95% limits of agreement and the coefficients of repeatability (CR) of IVC_d and PIF_d through the different inhalers were high and variable in both controls and patients. It is important to highlight that low CR represents better repeatability. Of note, the CR in COPD patients for IVC_d was the largest using Ellipta® followed by Respimat®. For PIF_d, CR was largest in Respimat®, followed by Chiesi®-pMDI in All-LF-COPD group.

4.1.5. Ranking of inhalers based on the differences between inspiratory parameters

Furthermore, we conducted a ranking of the four inhalers based in the differences observed between the two measurements of PIF_d and IVC_d, as depicted in Figure 6. This ranking provides insight into the inhalers that exhibited the smallest differences in parameters between the two inhalation maneuvers, denoted as Rank 1. Consistent with the findings based on the CR values in COPD patients, Respimat® and Genuair® demonstrated the least inter-measurement differences for IVC_d, while Ellipta® and Genuair® exhibited the lowest variability for PIF_d measurements.(108)

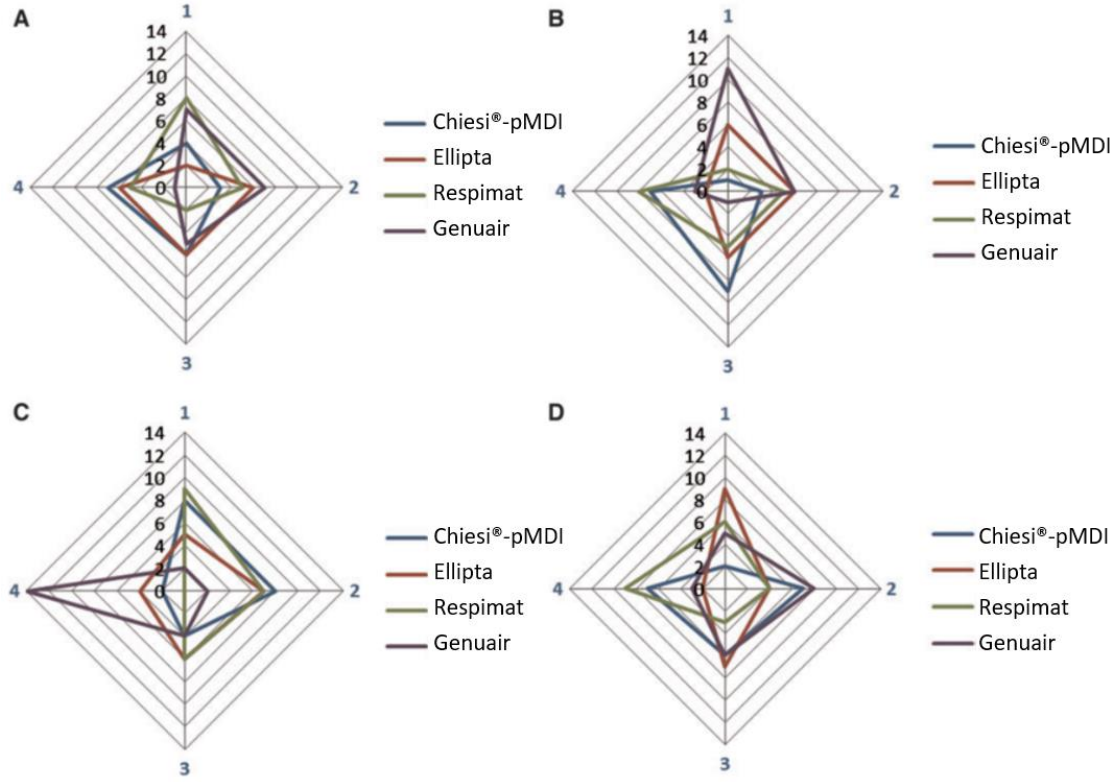

Figure 6. Repeatability sequence summary of through-device measurements for the four inhalers in Phase 1.

A: All-LF-COPD IVC_d (n=20). B: All-LF-COPD PIF_d (n=20). C: LF-Controls IVC_d (n=22). D: LF-Controls PIF_d (n=22). By each control subject and patient, a rank number between 1 and 4 was associated with each inhaler regarding the magnitude of the difference between the two values for PIF_d and IVC_d, respectively. Rank 1 was given to the device with the lowest difference between the two inspiratory measurements followed

by Rank 2, 3 and 4. On the figure, rank numbers are shown by 4 edges of the axes with blue color, and the sum of subjects with a certain rank are indicated on the axes. IVC_d: through-device inspiratory vital capacity; PIF_d: through-device peak inspiratory flow. Another version of this figure has been published in Erdelyi et al.(108)

4.2. Phase 2

4.2.1. Clinical characteristics of participants

A summary of the characteristics of both patients and control volunteers is provided in Table 10. It is observed that individuals diagnosed with COPD were notably older, had a higher prevalence of smoking, and had a greater cumulative smoking impact. All PD-COPD-AE patients met the criteria for GOLD 2015 D category. PD-COPD patients exhibited a significant number of comorbidities; however, there were no significant differences in this aspect between stable and exacerbated patients. Patients experiencing exacerbations displayed more symptoms based on mMRC, CAT® and VAS scores. The maintenance inhalation therapy was similar across patient groups, with the majority of patients receiving triple therapy.(109)

Table 10. Clinical characteristics of controls and patients in Phase 2.

	PD-Controls	PD-COPD-S	PD-COPD -AE
Number (n)	17	13	12
Female/male	10/7	9/4	9/3
Age (years)	43 ± 4	65 ± 2*	61 ± 2*
BMI (kg/m^2)	25.0 ± 0.9	25.6 ± 1.4	27.1 ± 2.0
Smoking habit, n (%)**			
Current smoker	8 (47)	4 (31)	7 (58)
Former smoker	1 (6)	9 (69)	5 (42)
Never smoker	8 (47)	0 (0)	0 (0)
Pack years	18 ± 5	50 ± 5*	36 ± 3*
GOLD category 2015, n (%)			
A	NA	1 (8)	0 (0)
B	NA	1 (8)	0 (0)
C	NA	5 (38)	0 (0)
D	NA	6 (46)	12 (100)
Quality of life			
mMRC	0 (0–0)[1]	2 (1–2)[2]*	4 (3–4)*
CAT®	2 (0–6)	11 (7–22)[2]*	27 (18–30)*
VAS	1 (0–3)[3]	5 (4–5)[2]*	8 (7–10)[4]*
Comorbidities, n (%)			
Osteoporosis	NA	0 (0)	3 (25)
Diabetes mellitus	NA	1 (8)	3 (25)
Hypertension	NA	4 (31)	2 (17)
Atherosclerosis	NA	4 (31)	4 (33)
Myocardial infarction	NA	0 (0)	2 (17)
Stroke	NA	0 (0)	2 (17)
Maintenance COPD therapy, n (%)			
ICS	NA	9 (69)	12 (100)
LABA	NA	12 (92)	12 (100)
LAMA	NA	12 (92)	12 (100)

Theophylline	NA	3 (23)	6 (50)

* $p < 0.05$ vs. PD-Control-s, ** Chi-square test: $p < 0.01$. [1]n = 16; [2]n = 10; [3]n = 15; [4]n = 11. BMI: Body Mass Index; CAT: COPD Assessment Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting $beta_2$-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council; NA: not applicable; PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD; VAS: Visual Analogue Scale. Data are shown as mean ± standard error of the mean (SEM) or median (interquartile range). Another version of this table has been published in Erdelyi et al.(109) (2023) Frontiers.

4.2.2. Lung function results

Table 11 provides information on LF parameters, indicating that both PD-COPD groups exhibited severe airflow obstruction and lung hyperinflation. In contrast, the PD-Controls group demonstrated normal LF parameters.(109)

Table 11. Lung function values in Phase 2.

	PD-Controls	PD-COPD-S	PD-COPD-AE
Number (n)	17	13	12
FVC, % predicted	102 ± 3	79 ± 6*	67 ± 7*
FEV_1, % predicted	95 ± 2	42 ± 5*	35 ± 5*
FEV_1/FVC, %	79 ± 2	44 ± 3*	49 ± 3*
PEF, % predicted	85 ± 8	41 ± 4*[1]	34 ± 3*[2]
$FEF_{25-75\%}$, % predicted	76 ± 5	18 ± 3*	17 ± 2*
PIF, L/s	5 ± 0.4	2 ± 0.1*	3 ± 0.3*
IVC, % predicted	99 ± 3	77 ± 5*	67 ± 5*
TLC, % predicted	93 ± 2	103 ± 5*	113 ± 8*
TGV, % predicted	119 ± 5	168 ± 11*	193 ± 15*
RV, % predicted	83 ± 6	152 ± 15*	192 ± 19*
RV/TLC	0.28 ± 0.02	0.56 ± 0.03*	0.66 ± 0.04*
Raw, % predicted	108 ± 6	295 ± 25*[1]	297 ± 31 *

* $p < 0.05$ vs. PD-Controls, [1]n=12, [2]n=13. $FEF_{25-75\%}$, forced expiratory flow at 25-75% of the pulmonary volume; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; IVC, inspiratory vital capacity; PEF, peak expiratory flow; PIF, peak inspiratory flow; Raw, airway resistance; RV, residual volume; PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD; TGV, thoracic gas volume; TLC, total lung capacity. Data are shown as mean ± standard error of the mean (SEM). Another version of this table has been published in Erdelyi et al.(109) (2023) Frontiers.

4.2.3. Through-device inhalation parameters using different inhalers

The results of testing IVC_d, PIF_d, t_{in}, and t_{bh} for both pMDI and SMI devices are presented in Table 12. In the control group, IVC_d was lower when measured with both devices compared to normal spirometry, while in both PD-COPD groups, it was only slightly lower. PIF_d was significantly lower in the PD-Controls group and both PD-COPD groups

compared to PIF during spirometry for both devices. The average t_{in} ranged between 2-3 seconds for all groups. Mean t_{bh} exceeded 10 seconds in the PD-Controls and PD-COPD-S groups, but was significantly lower in PD-COPD-AE patients compared to LF-COPD-S patients.(109)

Table 12. Spirometric and inhalation parameters measured through the different inhalers in Phase 2.

PD-Controls (n=17)		
Spirometry:	IVC (L)	4.02 ± 0.26
Spirometry:	PIF (L/s)	5.08 ± 0.36
	Chiesi®-pMDI	Respimat®
IVC_d (L)	3.36 ± 0.22*	3.61 ± 0.21*
PIF_d (L/s)	2.61 ± 0.22*	2.19 ± 0.15*
t_{in} (s)	2.23 ± 0.22	2.51 ± 0.23
t_{bh} (s)	9.95 ± 0.12	9.93 ± 0.16
PD-COPD-S (n=13)		
Spirometry:	IVC (L)	2.35 ± 0.2**
Spirometry:	PIF (L/s)	2.48 ± 0.15**
	Chiesi®-pMDI	Respimat®
IVC_d (L)	2.23 ± 0.17**	2.29 ± 0.21**
PIF_d (L/s)	1.80 ± 0.16*,**	1.48 ± 0.14*,**
t_{in} (s)	2.44 ± 0.26	2.57 ± 0.27
t_{bh} (s)	10.39 ± 0.1	10.57 ± 0.18
PD-COPD-AE (n=12)		
Spirometry:	IVC (L)	2.17 ± 0.25**
Spirometry:	PIF (L/s)	2.80 ± 0.32**
	Chiesi®-pMDI	Respimat®
IVC_d (L)	2.06 ± 0.23**	2.18 ± 0.21**
PIF_d (L/s)	1.79 ± 0.13*,**	1.48 ± 0.12*,**
t_{in} (s)	2.3 ± 0.28	2.52 ± 0.26

t_{bh} (s)	9.55 ± 0.16***	9.44 ± 0.40***

IVC: inspiratory vital capacity; PIF: peak inspiratory flow; IVC_d: through-device inspiratory vital capacity; PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD; PIF_d: through-device peak inspiratory flow; t_{in}: inhalation time; t_{bh}: breath hold time; *p<0.05 vs. values obtained by standard spirometry; **p<0.05 vs. PD-Controls; ***p<0.05 vs. PD-COPD-S. Data are shown as mean ± standard error of the mean (SEM). Another version of this table has been published in Erdelyi et al. (109) (2023) Frontiers.

4.2.4. Pulmonary (PD) and extrathoracic deposition (ETD)

The results of numerical modeling for Foster® pMDI, Trimbow® pMDI and Spiriva® Respimat® are summarized in Figures 7 and 8. Both PD-COPD groups and PD-Controls exhibited significant differences when comparing the results of Spiriva® Respimat® to the two pMDIs in terms of PD and ETD. Spiriva® Respimat® resulted in significantly higher PD compared to Foster® pMDI and Trimbow® pMDI. For Foster® pMDI and Trimbow® pMDI, similar PD values were observed in PD-Controls, while ETD between PD-Controls and PD-COPD-AE patients showed a significant difference. ETD values were significantly lower in all PD-COPD patients compared to healthy volunteers. Spiriva® Respimat® demonstrated significantly lower ETD values than Foster® pMDI and Trimbow® pMDI.(109)

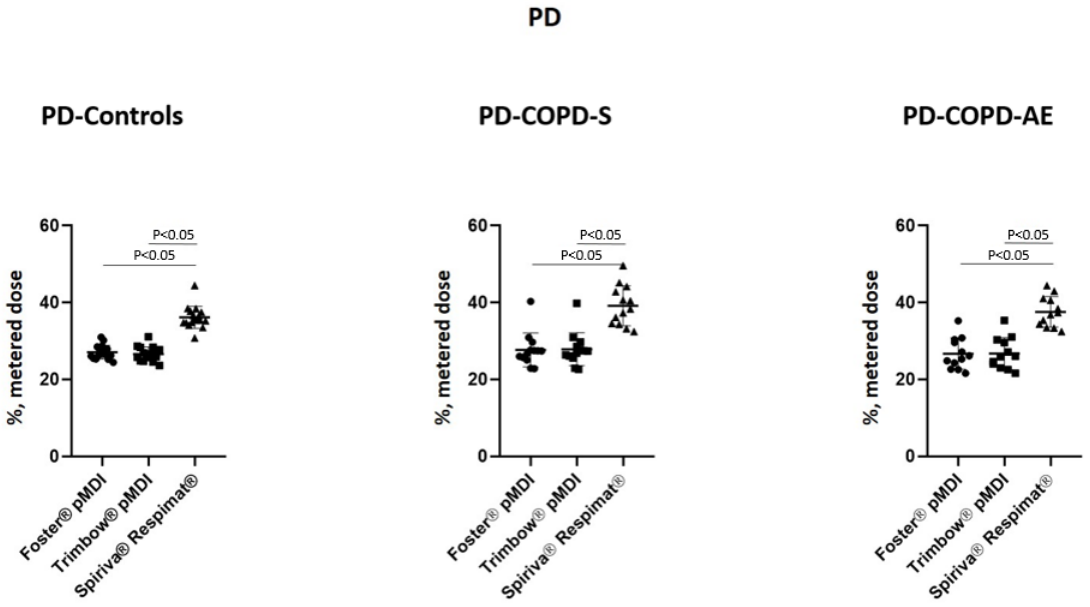

Figure 7. Pulmonary deposition (PD). PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD. Another version of this figure has been published in Erdelyi et al.(109) (2023) Frontiers.

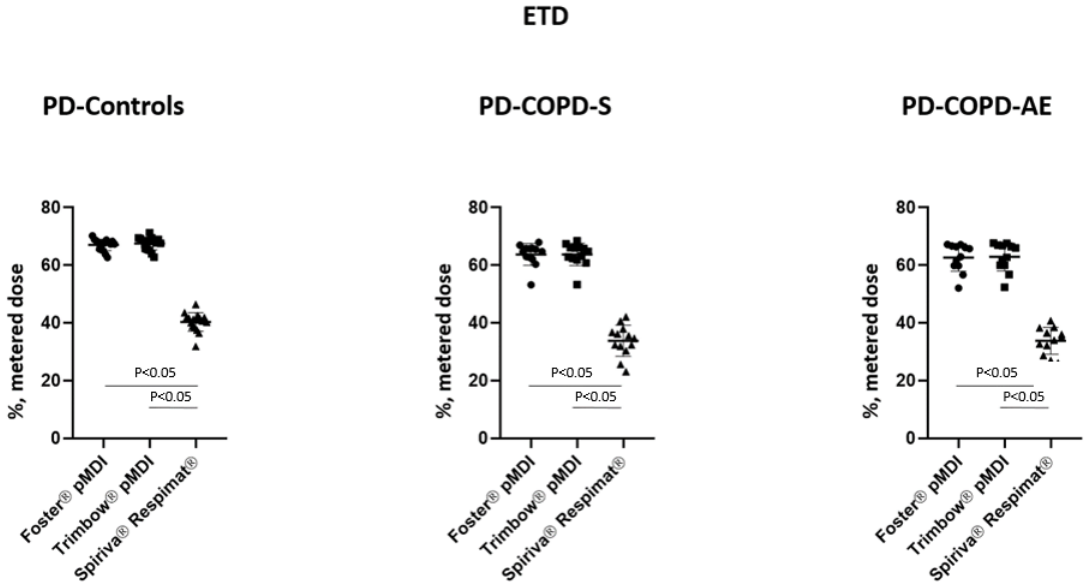

Figure 8. Extrathoracic deposition (ETD). PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD. Another version of this figure has been published in Erdelyi et al.(109) (2023) Frontiers.

4.2.5. Repeatability of PD and ETD values calculated from repeated measurements

To assess the variability of PD and ETD values calculated from inhalation maneuver parameters and particle size distribution, the Bland-Altman analysis was employed. Significant individual differences were observed for all tested medications in terms of PD and ETD, as depicted in Figures 9 and 10. The X-axis represents the mean of the two calculations for deposition values, while the Y-axis represents the difference between the two calculated values from repeated measurements (1st measurement - 2nd measurement). Moreover, the bias (the difference between the X-axis and the average mean of the two calculations for all subjects) was calculated for PD and ETD in PD-Controls, PD-COPD-S and PD-COPD-AE groups for each inhaler. It was found that PD was significantly higher in the values calculated from the second measurements in PD-Controls using Foster® pMDI and Trimbow® pMDI. There was a tendency for the second value to be higher in healthy volunteers using Spiriva® Respimat®. No significant difference between the two values was observed in either PD-COPD group for the two pMDI devices, but in PD-COPD-S patients, the second value tended to be lower, while in PD-COPD-AE patients, it tended to be higher.

The 95% limits of agreement and coefficients of repeatability (CR) for PD and ETD with different inhalers were high and varied in both control subjects and patients. It is important to note that a low CR indicates better repeatability. Notably, the CR for PD in PD-COPD-S and PD-COPD-AE patients was highest when using Trimbow® pMDI. The results are presented in Table 13 (one-sample t-test).(109)

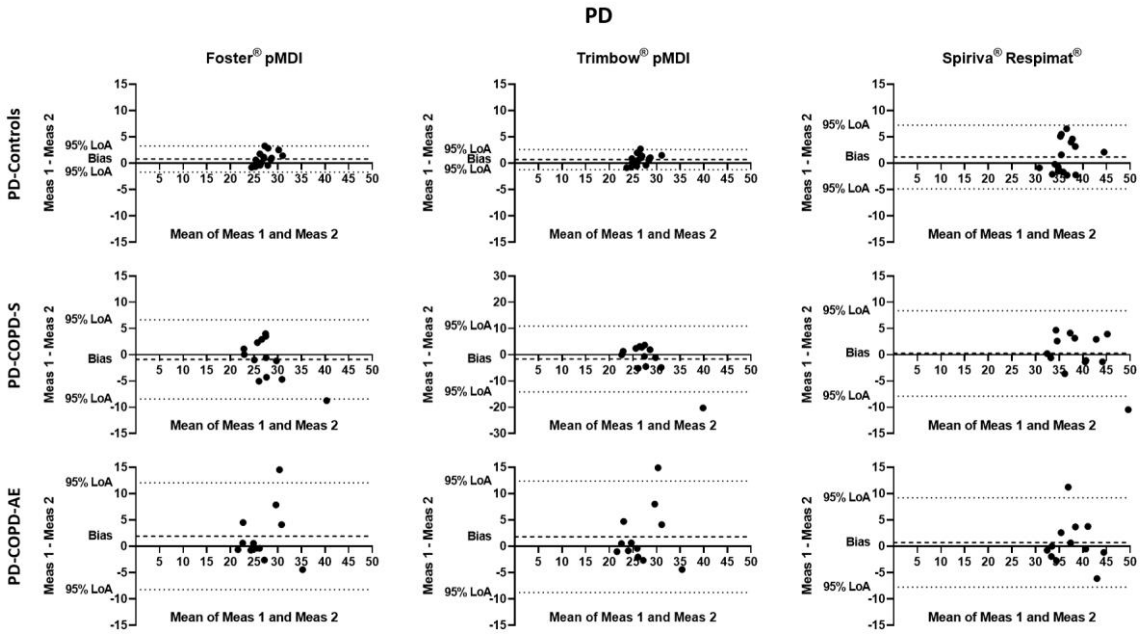

Figure 9. Bland-Altman analysis of pulmonary deposition (PD). The X-axis represents the mean of the two measurements for PD, while the Y-axis shows the difference of the repeated measurements (first measurement–second measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects. LoA, Bland-Altman 95% limits of agreement; Meas, measurement; PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD. Another version of this figure has been published in Erdelyi et al.(109) (2023) Frontiers.

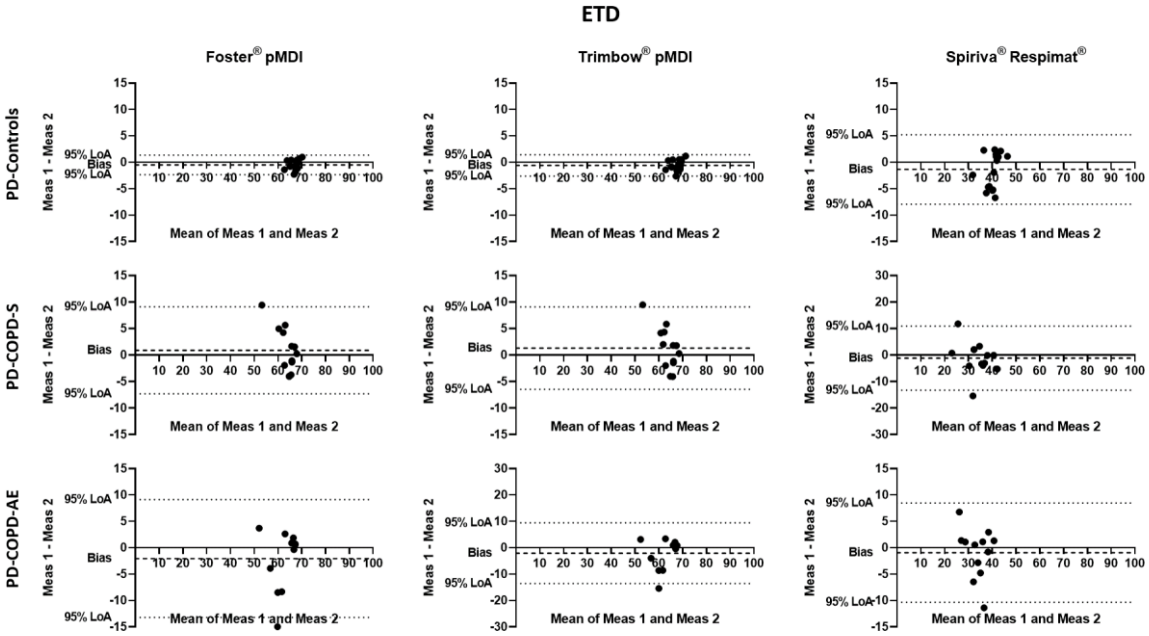

Figure 10. Bland-Altman analysis of extrathoracic deposition (ETD). The X-axis represents the mean of the two measurements for PD, while the Y-axis shows the difference of the repeated measurements (first measurement–second measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects. LoA, Bland-Altman 95% limits of agreement; Meas, measurement; PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S: patients with stable COPD. Another version of this figure has been published in Erdelyi et al.(109) (2023) Frontiers.

Table 13. Repeatability of PD and ETD values calculated from repeated measurements.

			PD-Controls		
	n	Bias	p*	95% LoA	CR
PD					
Foster® pMDI	17	0.80	**0.02**	-1.68 – 3.28	2.87
Trimbow® pMDI	17	0.70	**0.005**	-1.21 – 2.61	2.31
Spiriva® Respimat®	17	1.19	0.13	-4.86 – 7.23	6.31
ETD					
Foster® pMDI	17	-0.5	**0.046**	-2.35 – 1.36	2.05
Trimbow® pMDI	17	-0.59	**0.032**	-2.62 – 1.44	2.29
Spiriva® Respimat®	17	-1.35	0.12	-7.93 – 5.22	6.91
			PD-COPD-S		
	n	Bias	p*	95% LoA	CR
PD					
Foster® pMDI	13	-0.89	0.42	-8.45 – 6.67	7.47
Trimbow® pMDI	13	-1.62	0.38	-14.2 – 10.91	12.46
Spiriva® Respimat®	13	0.25	0.83	-7.89 – 8.39	7.84
ETD					
Foster® pMDI	13	0.89	0.46	-7.32 – 9.11	8.08
Trimbow® pMDI	13	1.31	0.26	-6.46 – 9.08	7.9
Spiriva® Respimat®	13	-1.17	0.51	-13.28 – 10.94	11.86
			PD-COPD-AE		
	n	Bias	p*	95% LoA	CR
PD					
Foster® pMDI	12	1.91	0.23	-8.24 – 12.06	10.42
Trimbow® pMDI	12	1.8	0.27	-8.78 – 12.38	10.72
Spiriva® Respimat®	12	0.72	0.58	-7.77 – 9.21	8.25
ETD					
Foster® pMDI	12	-2.06	0.24	-13.22 – 9.1	11.42
Trimbow® pMDI	12	-2.07	0.25	-13.57 – 9.43	11.74
Spiriva® Respimat®	12	-0.93	0.52	-10.34 – 8.47	9.19

CR: coefficients of repeatability; LoA: Bland-Altman 95% limits of agreement; n, number of subjects; PD-COPD-AE: patients with exacerbated COPD; PD-COPD-S:

patients with stable COPD. Significant differences are highlighted in bold. *p<0.05 for one-sample t-test of the bias. Another version of this table has been published in Erdelyi et al.(109) (2023) Frontiers.

4.2.6. Ranking of inhalers based on the differences between deposition values

Figure 11 presents the ranking of the three inhalers based on the differences between the two values of PD. The inhalers are ranked from smallest to largest difference, with Rank 1 indicating the inhaler with the smallest difference, followed by Rank 2 and Rank 3. Consistent with the findings based on the CR values in patients with COPD, Respimat® demonstrated the smallest differences between the two deposition results for PD.

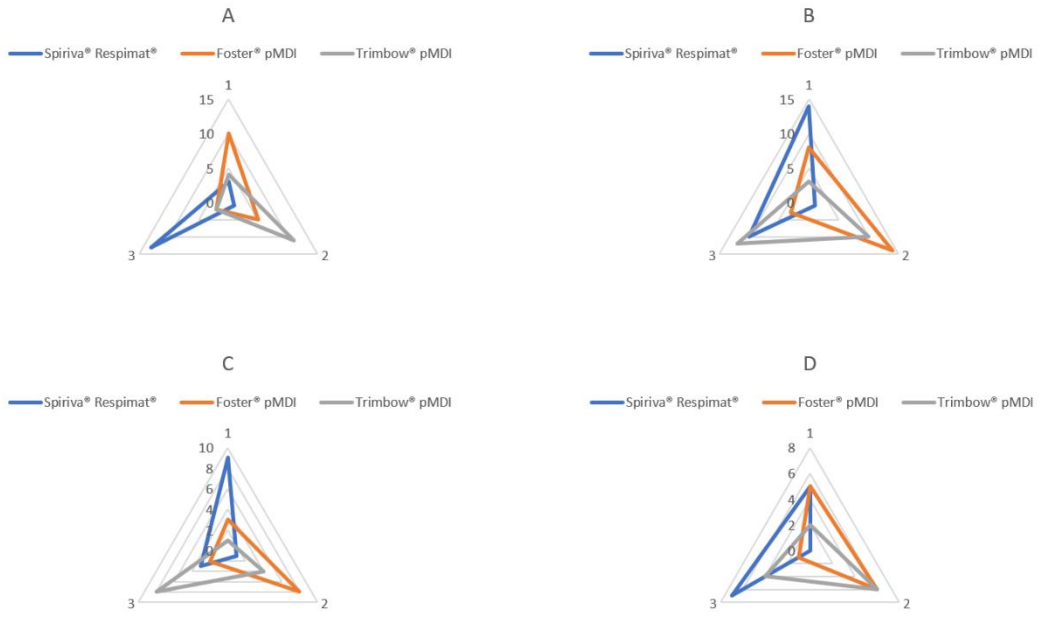

Figure 11. Repeatability sequence summary of pulmonary deposition (PD) for the three inhalers of Phase 2.

A: PD-Controls: healthy volunteers (n = 17); B: All-PD-COPD: patients with stable and exacerbated COPD (n=25); C: PD-COPD-S: patients with stable COPD (n=13); D: PD-COPD-AE: patients with exacerbated COPD (n=12). By each control subject and patient, a rank number between 1 and 3 was associated with each inhaler regarding the magnitude of the difference between the two values for PD, respectively. Rank 1 was given to the

device with the lowest difference between the two inspiratory measurements followed by Rank 2 and 3. On the figure, rank numbers are shown by three edges of the axes, and the sum of subjects with a certain rank is indicated on the axes. COPD: chronic obstructive pulmonary disease. Another version of this figure has been published in Erdelyi et al.(109) (2023) Frontiers.

5. DISCUSSION

Our work is the first that examined inhalation maneuvers, pulmonary deposition and their repeatability in stable and exacerbated COPD patients. Four commercially available inhaler devices (Chiesi®-pMDI, Ellipta®, Genuair® and Respimat®) were compared regarding inhalation parameters and repeatability. The importance of correct inhaler uses and proper lung deposition is inevitable, however, intraindividual variability may indicate inconsistent pulmonary drug delivery and therapeutical effectiveness.(84, 113)

Achieving appropriate inhalation technique can be difficult especially in severe COPD patients as in the last 40 years errors persist. (114, 115) Regular inhaler training is also underlined in international guidelines in asthma and COPD patients.(1, 2) Low adherence in inhalation therapy in COPD might lead to symptom variability therefore correct and detailed training is needed by a respiratory specialist.(1, 114, 116, 117) Furthermore, patients' preferences of inhaler devices might vary.(118)

Inhaler performance is generally modeled by using individual differences of inhalation breath profiles.(84, 119) Pulmonary drug deposition is affected by inhalation parameters from which the most significant are IVC_d, PIF_d and t_{in}. PIF_d influences MMAD playing a crucial role in effective inhalation therapy in DPIs since MMAD is unfixed in such inhalers. MMAD can be determined by a cascade impactor using different flow rates.(94, 113) Intraindividual and interinhalation differences in inhalation parameters can highly influence deposition performance resulting an alteration in therapeutic response.(94) During modeling pulmonary drug delivery breath-hold time is responsible for the fraction particles deposited by diffusion, however, in our highly controlled setup, time of breath-hold directed by the examiner showed no significant differences.

Feldman et al. investigated LF improvements in COPD patients using LABA-LAMA combination from Ellipta® compared with Respimat® showing differences in particular patients applying two different inhalers.(120) As our subjects performed repeated measurements in all four devices, variability was evaluated by repeatability measurements using Bland-Altman plot. We found significant individual differences in all four devices in LF-Controls and all LF-COPD patients. In LF-Controls significant difference was noted in PIF_d through Chiesi®-pMDI and Respimat® which can be explained by the limited experience of inhaler use by these healthy subjects and, as well,

inspiratory muscle function could be better in this group. In Bland-Altman analysis, higher CR values refer to worse repeatability as this can be observed in LF-COPD patients in PIF_d and IVC_d, however, the associated biases were not found to be significant which might be the consequence of previous experience in the use of different inhaler devices. Intrasubject repeatability of breath profiles is a meaningful influencing factor of therapeutical effectiveness as established based our and previous data.(121) Pulmonary drug deposition is determined by many aspects such as drug formulation, inhaler type or the quality of the produced aerosol as well as its sensitivity to breath profile.(121-126) Further characteristics of different inhalers may change the therapeutic response, for example quality attributes to inhaler performance. Our study examined an important factor: repeatability of inhalation maneuvers, which might lead to insufficient therapeutic effectiveness when patients are not able to perform similarly by usage of inhalers, especially those that must be twice consecutively according to its summary of product characteristics (SmPCs). However, our work has its limitations, investigating the repeatability of inhaler performance should be emphasized further as it may result in better inhalation therapy.

Patients' preferences vary regarding inhalers by many aspects. We ranked four different inhalers frequently prescribed in COPD patients regarding their repeatability. Through-device inhaler performance showed individual differences in IVC_d and PIF_d. We found that most patients reached the best ranking in IVC_d using Genuair® and Respimat®, however, these inhalers ended up at the third or fourth place in some COPD patients highlighting the individual differences in inhaler performance. The best rankings were provided by Ellipta® and Genuair® regarding PIF_d, showing marked intrasubject differences. Our data supported the suggestion of the international recommendations as switching to another inhaler device or molecule in the same group as no therapeutical improvement is observable.(2) Nonetheless, no recommendation is available about the specific devices or molecules on which more emphasis should be placed.

AEs of COPD are challenging for the clinician in choosing the right medication and inhaler. During AE patients suffer from symptom worsening and decrease in LF parameters. Patient admission should contain assessing inhaler use by the patient as it is difficult to measure the role of a possible technique error or non-compliance in development of AEs. Many patients treated by inhalation therapy are already given a

triple combination of ICS, LABA and LAMA, either in an open triple therapy or an FDTC. Despite the high intensity of inhalation regime, our patients were symptomatic in most cases. One of the main aims of therapy is symptom relief as it improves quality of life and may help increasing adherence of the patients. It is important for patients to have an additional option even if the therapeutic maximum has already been reached.

We compared commercially available pMDIs (Foster®-pMDI and Trimbow®-pMDI) and one SMI (Spiriva® Respimat®) in COPD patients in order to evaluate the possible differences between and FDTC (ICS-LABA-LAMA) and open triple therapy (ICS-LABA pMDI and LAMA SMI). Stochastic Lung Model applied in our work was validated by the following publications as our results tended to be very similar, numerical modeling presented ~25-28% pulmonary drug deposition in our model for pMDI while comparable results were performed by gamma scintigraphy using active agents from Trimbow®-pMDI in asthma patients and healthy subjects.(127) Another study investigated Respimat® by gamma scintigraphy in COPD patients and PD showed quite similar results to our modeling (~37% vs. 36-39%).(74)

Previous scintigraphy studies showed that there was no significant difference in pulmonary drug deposition using Trimbow®-pMDI between asthma patients with mild airway obstruction and healthy controls.(127) Contrary to asthma patients, in COPD patients there is no available scintigraphy results of PD regarding FDTCs or open triple therapies. Our model was able to compare an FDTC and an open triple therapy, though it is not able to differentiate central and peripheral lung regions as gamma scintigraphy. Nonetheless, numerical modeling might be more advantageous compared to scintigraphy as it is safe and easily reproducible. We were able to assess PD in stable and acute exacerbated COPD patients by numerical modeling. The most important finding of our measurements is the similarity of PD value between PD-COPD-S and PD-COPD-AE as there was no significant difference for both low resistance pMDIs and SMI. Furthermore, we placed greater emphasis on repeatability as all three inhaled medications require two consecutive maneuvers according to their SmPCs, therefore we chose Foster®-pMDI and Trimbow®-pMDI and Spiriva® Respimat® as low resistance inhaler devices for our study.(128-130)

The role of FDTCs in inhalation therapy has been risen in the last few years providing a great option for the clinician in choosing the right device as one inhaler contains the three

main medication of COPD maintenance therapy. TRINITY study investigated Trimbow®-pMDI versus an open triple therapy and the FDTC showed non-inferiority regarding moderate-to-severe exacerbation rates and pre-dose FEV_1 for week 52.(131) However, TRINITY study used Spiriva® Handihaler® as the component containing LAMA while our investigation applied Spiriva® Respimat® which is a low-resistance device contrary to Handihaler® DPI.(131) Combination of two low-resistance inhaler devices in an open triple therapy might produce higher PD in stable and exacerbated patients and lead to better therapeutic effectiveness even in cases when the patient is not able to profit more from an FDTC. Switching from an FDTC to open triple therapy may present difficulties to patients by using two different devices, however it provides additional choice to the clinician and the patient as well. It is important to mention that in case of giving new device to a patient accurate education from a respiratory specialist is needed.

Contrary to the fact, that inhalation devices are suitable for patients with reduced LF parameters, inhalation performance might be decreased.(132) One of the most significant factor that worsens patients' capability to perform sufficient inhalation maneuvers is an AE of COPD. During exacerbation reduced inspiratory effort can be observed and LF parameters are impaired leading to possibly incoherent inhalation performance and a consequence, unstable pulmonary drug delivery. Nonetheless, our results showed no significant difference between stable and exacerbated patients using SMI and pMDI devices. Therefore, according to our result exacerbations did not influence pulmonary drug delivery negatively. This might be explained that inhaler technique is consistently checked during patient examination by stable and exacerbated patients as well.

Previous investigations confirmed the importance of device handling in the effectiveness of inhaled therapy. It is simple to understand that the use of more than one inhaler device in COPD can worsen adherence to inhalation therapy.(133-135) For patients with impaired LF low resistance inhaler devices are suggested as they are not able to produce efficient inspiratory effort.(136, 137) Inhaler manufacturers usually rely on the value of peak inspiratory flow to check whether the patients are capable of performing sufficient inhalation performance, however, a recently debated parameter which might be examined later is pressure drop,(77) though our study did not contain its investigation. Despite the importance of reducing the number of inhalers during COPD inhalation therapy, our

results suggest that patients might profit -considering pulmonary drug delivery – from switching from a single inhaler FDTC to an open triple therapy combining to low resistance inhalers.

Achieving correct inhalation technique and inhaler use, COPD patients, especially with impaired LF require appropriate education. Regular assessment of inhaler technique is needed in stable and exacerbated COPD patients during care.(138, 139) Severe COPD patients suffer from AEs frequently and during symptom worsening and hospitalization device handling might be more complicated. Our results show that an SMI can produce even pulmonary delivery in exacerbated patients. The significance of investigating measurement methods is underlined by repeatability. However, researching repeatability can show us differences in measurements performed by the same examiner on the same subjects, comparing different measurement methods carried out by separate examiners might place greater emphasis on reproducibility.(140)

DPI devices may not be applied effectively in patients with reduced LF parameters, therefore the use of low resistance inhalers such as pMDIs and DPIs should be highlighted in severe COPD patients.(141)

6. CONCLUSIONS

1. Comparing LF parameters through four commercially available inhaler devices showed that in healthy controls and exacerbated COPD patients produced significantly lower PIFd values comparing with standard spirometry values. Genuair® showed significantly lower PIFd in stable COPD.
2. The repeatability of inhalation parameters revealed that no significant difference was observed in COPD patients, only in healthy subjects having a lack of experience in inhaler use. However, patients showed individual alterations regarding the difference of the two inhalations through the tested devices.
3. Significantly higher PD and lower ETD values were produced by Spiriva® Respimat ® showed values comparing with Foster® -PMDI and Trimbow® - pMDI. Our results emphasize that in case of severe COPD patients clinicians can switch from FDTCs to open triple low-resistance inhaler therapy in order to achieve higher deposition of inhaled agents.
4. The repeatability of PD and ETD revealed that FDTC showed the highest CR indicating the lowest repeatability. Individual differences were observed in pulmonary deposition in the three commercially available inhalers.

7. SUMMARY

Inhalation therapy is the cornerstone of obstructive airway disorders including COPD and improving the effectiveness of inhalation may increase therapeutic response using inhaled agents, in most cases ICS and bronchodilators in COPD therapeutical regime. In order to perfect inhaled therapy many factors relying on the patients' capabilities, devices' characteristics and the agents' qualities should be taken into consideration.

Our study aimed to assess the inhalation maneuvers, PD and repeatability of inhalation parameters and deposition using inhaler devices in stable and exacerbated COPD patients. While no significant differences were observed regarding standard spirometry and body plethysmography COPD patients presented severely impaired LF parameters. Through-device LF parameters were measured using four commercially available inhaler devices: Chiesi®-pMDI, Ellipta®, Genuair® and Respimat® uniquely in the international literature. Inhalation parameters as PIF_d were compared and highlighted that Genuair® showed significantly lower values suggesting that DPIs may not be the proper devices for all patients. As an often not sufficiently emphasized factor repeatability is crucial for a stable therapeutical effectiveness, however, it presented no significant differences in COPD patients. Individual variances were observed regarding devices interpreting differences between two inhalations.

PD and its improvement are essential to enhance therapy and our work examined three commercially available low-resistance inhaler devices using numerical modeling technique. Our study implies that in certain cases patients may benefit from switching from and FDTC to open triple low-resistance inhaler therapy. Obviously, patients' preferences should be taken into consideration and regular patient education should be maintained by a physician. Similar to inhalation parameters, deposition values showed individual differences between two inhalations in the tested devices and the rate of repeatability tended to be different in inhalers.

Our work is the first study emphasizing the importance of repeatability of inhaler use in severe COPD patients and healthy subjects and compared the deposition of an FDTC and open triple therapy in three low-resistance inhaler devices. Our study might help to further improve patient care and this already quickly developing field of COPD therapy.

8. REFERENCES

1. GINA. Global Strategy for Asthma Management and Prevention. Available from wwwginasthmaorg. 2022.
2. GOLD. Global Strategy for Diagnosis, Management and Prevention of COPD. Available from wwwgoldcopdorg. 2022.
3. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. The European respiratory journal. 2006;27(2):397-412.
4. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic D, Sridhar D, Campbell H, Chan KY, Sheikh A, Rudan I. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. Journal of global health. 2015;5(2):020415.
5. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. The Lancet Respiratory medicine. 2022;10(5):447-58.
6. Bui DS, Perret JL, Walters EH, Lodge CJ, Bowatte G, Hamilton GS, Thompson BR, Frith P, Erbas B, Thomas PS, Johns DP, Wood-Baker R, Hopper JL, Davis PG, Abramson MJ, Lowe AJ, Dharmage SC. Association between very to moderate preterm births, lung function deficits, and COPD at age 53 years: analysis of a prospective cohort study. The Lancet Respiratory medicine. 2022;10(5):478-84.
7. Diette GB, Accinelli RA, Balmes JR, Buist AS, Checkley W, Garbe P, Hansel NN, Kapil V, Gordon S, Lagat DK, Yip F, Mortimer K, Perez-Padilla R, Roth C, Schwaninger JM, Punturieri A, Kiley J. OBSTRUCTIVE LUNG DISEASE AND EXPOSURE TO BURNING BIOMASS FUEL IN THE INDOOR ENVIRONMENT. Global heart. 2012;7(3):265-70.
8. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British medical journal. 1977;1(6077):1645-8.
9. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. Lancet (London, England). 2022;399(10342):2227-42.

10. Wang Y, Xu J, Meng Y, Adcock IM, Yao X. Role of inflammatory cells in airway remodeling in COPD. International journal of chronic obstructive pulmonary disease. 2018;13:3341-8.
11. van der Schans CP. Therapy for Mucus-clearance Disorders: Marcel Dekker; 2004.
12. Jones PW, Watz H, Wouters EF, Cazzola M. COPD: the patient perspective. International journal of chronic obstructive pulmonary disease. 2016;11 Spec Iss(Spec Iss):13-20.
13. Murgia N, Gambelunghe A. Occupational COPD-The most under-recognized occupational lung disease? Respirology (Carlton, Vic). 2022;27(6):399-410.
14. Laucho-Contreras ME, Cohen-Todd M. Early diagnosis of COPD: myth or a true perspective. European respiratory review : an official journal of the European Respiratory Society. 2020;29(158).
15. Price D, Brusselle G. Challenges of COPD diagnosis. Expert opinion on medical diagnostics. 2013;7(6):543-56.
16. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93(3):580-6.
17. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. The European respiratory journal. 1995;8(3):492-506.
18. Puente-Maestu L, Stringer WW. Hyperinflation and its management in COPD. International journal of chronic obstructive pulmonary disease. 2006;1(4):381-400.
19. Kaminsky D. The Netter Collection of Medical Illustrations: Respiratory System, 2nd Edn. . 2011.
20. Losonczy G, Müller V, Horváth G, Tamási L. Pulmonológia. Budapest: Medicina Zrt. ; 2020.
21. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clinical interventions in aging. 2006;1(3):253-60.
22. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. The European respiratory journal. 1999;13(1):197-205.

23. GOLD. Global Strategy for Diagnosis, Management and Prevention of COPD. Available from wwwgoldcopdorg. 2015.
24. Llewellin P, Sawyer G, Lewis S, Cheng S, Weatherall M, Fitzharris P, Beasley R. The relationship between FEV1 and PEF in the assessment of the severity of airways obstruction. Respirology (Carlton, Vic). 2002;7(4):333-7.
25. Amariei DE, Dodia N, Deepak J, Hines SE, Galvin JR, Atamas SP, Todd NW. Combined Pulmonary Fibrosis and Emphysema: Pulmonary Function Testing and a Pathophysiology Perspective. Medicina (Kaunas, Lithuania). 2019;55(9).
26. GOLD. Global Strategy for Diagnosis, Management and Prevention of COPD. . Available from wwwgoldcopdorg. 2023.
27. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. The European respiratory journal. 2009;34(3):648-54.
28. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68(11):1029-36.
29. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2014;2014(3):Cd010115.
30. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. The New England journal of medicine. 2007;356(8):775-89.
31. Anderson PJ. History of aerosol therapy: liquid nebulization to MDIs to DPIs. Respiratory care. 2005;50(9):1139-50.
32. Cazzola M, Ora J, Calzetta L, Rogliani P, Matera MG. The future of inhalation therapy in chronic obstructive pulmonary disease. Current research in pharmacology and drug discovery. 2022;3:100092.
33. Rancati F, Linney ID, Rizzi A, Delcanale M, Knight CK, Schmidt W, Pastore F, Riccardi B, Mileo V, Carnini C, Cesari N, Blackaby WP, Patacchini R, Carzaniga L. Discovery of a novel class of inhaled dual pharmacology muscarinic antagonist and β(2) agonist (MABA) for the treatment of chronic obstructive pulmonary disease (COPD). Bioorganic & medicinal chemistry letters. 2021;41:127975.

34. Singh D, Lea S, Mathioudakis AG. Inhaled Phosphodiesterase Inhibitors for the Treatment of Chronic Obstructive Pulmonary Disease. Drugs. 2021;81(16):1821-30.
35. Nixon J, Newbold P, Mustelin T, Anderson GP, Kolbeck R. Monoclonal antibody therapy for the treatment of asthma and chronic obstructive pulmonary disease with eosinophilic inflammation. Pharmacology & therapeutics. 2017;169:57-77.
36. Sriskantharajah S, Hamblin N, Worsley S, Calver AR, Hessel EM, Amour A. Targeting phosphoinositide 3-kinase δ for the treatment of respiratory diseases. Annals of the New York Academy of Sciences. 2013;1280:35-9.
37. Billington CK, Penn RB, Hall IP. β(2) Agonists. Handbook of experimental pharmacology. 2017;237:23-40.
38. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. European Respiratory Journal. 2017;49(3):1600791.
39. Kollégium ES. Egészségügyi szakmai irányelv – A krónikus obstruktiv tüdőbetegség (chronic obstructive pulmonary disease – COPD) diagnosztikájáról, kezeléséről és gondozásáról Egészségügyi Közlöny, elérhető: https://kollegiumaeekhu. 2020.
40. Beeh KM, Beier J. The short, the long and the "ultra-long": why duration of bronchodilator action matters in chronic obstructive pulmonary disease. Advances in therapy. 2010;27(3):150-9.
41. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. American journal of respiratory and critical care medicine. 1997;155(4):1283-9.
42. Man SF, McAlister FA, Anthonisen NR, Sin DD. Contemporary management of chronic obstructive pulmonary disease: clinical applications. Jama. 2003;290(17):2313-6.
43. Roffel AF, Elzinga CR, Zaagsma J. Muscarinic M3 receptors mediate contraction of human central and peripheral airway smooth muscle. Pulmonary pharmacology. 1990;3(1):47-51.

44. Matera MG, Cazzola M. Muscarinic Receptor Antagonists. Handbook of experimental pharmacology. 2017;237:41-62.
45. Barnes PJ. Bronchodilators: Basic Pharmacology. In: Calverley PMA, Pride NB, editors. Chronic Obstructive Pulmonary Disease. Boston, MA: Springer US; 1995. p. 391-417.
46. Melani AS. Long-acting muscarinic antagonists. Expert review of clinical pharmacology. 2015;8(4):479-501.
47. Gross NJ. Ipratropium bromide. The New England journal of medicine. 1988;319(8):486-94.
48. Lipson DA. Tiotropium bromide. International journal of chronic obstructive pulmonary disease. 2006;1(2):107-14.
49. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2012(7):Cd009285.
50. Calzetta L, Ritondo BL, Zappa MC, Manzetti GM, Perduno A, Shute J, Rogliani P. The impact of long-acting muscarinic antagonists on mucus hypersecretion and cough in chronic obstructive pulmonary disease: a systematic review. European respiratory review : an official journal of the European Respiratory Society. 2022;31(164).
51. Katsumata M, Fujisawa T, Kamiya Y, Tanaka Y, Kamiya C, Inoue Y, Hozumi H, Karayama M, Suzuki Y, Furuhashi K, Enomoto N, Nakamura Y, Inui N, Maekawa M, Setou M, Watanabe H, Ikegami K, Suda T. Effects of long-acting muscarinic antagonists on promoting ciliary function in airway epithelium. BMC pulmonary medicine. 2022;22(1):186.
52. Packe GE, Cayton RM, Mashhoudi N. Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. Lancet (London, England). 1984;2(8404):691.
53. Raissy HH, Kelly HW, Harkins M, Szefler SJ. Inhaled corticosteroids in lung diseases. American journal of respiratory and critical care medicine. 2013;187(8):798-803.
54. Loppow D, Schleiss MB, Kanniess F, Taube C, Jörres RA, Magnussen H. In patients with chronic bronchitis a four week trial with inhaled steroids does not attenuate airway inflammation. Respiratory medicine. 2001;95(2):115-21.

55. Müller V, Horváth G, Tamási L, Eszes N, Bohács A, Vincze K, Kováts Z, Lázár Z, Odler B, Kornafeld A, Erdélyi T, Somogyi V, Losonczy G. Obstruktív tüdőbetegségekben alkalmazott inhalációs gyógyszerek célpontjai: receptorok a légúti felszín sejtjein. Medicina Thoracalis. 2015;1:6-12.

56. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2012;2012(9):Cd006829.

57. Koarai A, Yamada M, Ichikawa T, Fujino N, Kawayama T, Sugiura H. Triple versus LAMA/LABA combination therapy for patients with COPD: a systematic review and meta-analysis. Respiratory Research. 2021;22(1):183.

58. Dobler CC. The IMPACT of triple versus dual single-inhaler therapy on exacerbations of COPD. Breathe (Sheffield, England). 2018;14(4):333-5.

59. Buchman AL. Side effects of corticosteroid therapy. Journal of clinical gastroenterology. 2001;33(4):289-94.

60. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. The American journal of medicine. 1995;98(2):196-208.

61. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2012;2012(7):Cd002991.

62. Crim C, Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, Wachtel A, Martinez FJ, Barnhart F, Lettis S, Calverley PM. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. Annals of the American Thoracic Society. 2015;12(1):27-34.

63. Rees PJ, Clark TJ, Morén F. The importance of particle size in response to inhaled bronchodilators. European journal of respiratory diseases Supplement. 1982;119:73-8.

64. Pleasants RA, Hess DR. Aerosol Delivery Devices for Obstructive Lung Diseases. Respiratory care. 2018;63(6):708.

65. Dailey PA, Shockley CM. Review of aerosol delivery in the emergency department. Annals of translational medicine. 2021;9(7):591.

66. Ari A. Jet, Ultrasonic, and Mesh Nebulizers: An Evaluation of Nebulizers for Better Clinical Outcomes. Euras J Pulm. 2014;16:1-7.

67. Freedman T. Medihaler therapy for bronchial asthma; a new type of aerosol therapy. Postgraduate medicine. 1956;20(6):667-73.
68. Stein SW, Thiel CG. The History of Therapeutic Aerosols: A Chronological Review. J Aerosol Med Pulm Drug Deliv. 2017;30(1):20-41.
69. Newman SP. Principles of metered-dose inhaler design. Respiratory care. 2005;50(9):1177-90.
70. Myrdal PB, Sheth P, Stein SW. Advances in metered dose inhaler technology: formulation development. AAPS PharmSciTech. 2014;15(2):434-55.
71. McDonald KJ, Martin GP. Transition to CFC-free metered dose inhalers — into the new millennium. International Journal of Pharmaceutics. 2000;201(1):89-107.
72. Rogliani P, Calzetta L, Coppola A, Cavalli F, Ora J, Puxeddu E, Matera MG, Cazzola M. Optimizing drug delivery in COPD: The role of inhaler devices. Respiratory medicine. 2017;124:6-14.
73. De Backer W, Devolder A, Poli G, Acerbi D, Monno R, Herpich C, Sommerer K, Meyer T, Mariotti F. Lung deposition of BDP/formoterol HFA pMDI in healthy volunteers, asthmatic, and COPD patients. J Aerosol Med Pulm Drug Deliv. 2010;23(3):137-48.
74. Brand P, Hederer B, Austen G, Dewberry H, Meyer T. Higher lung deposition with Respimat Soft Mist inhaler than HFA-MDI in COPD patients with poor technique. International journal of chronic obstructive pulmonary disease. 2008;3(4):763-70.
75. Mahler DA. Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in Chronic Obstructive Pulmonary Disease. Annals of the American Thoracic Society. 2017;14(7):1103-7.
76. Telko MJ, Hickey AJ. Dry powder inhaler formulation. Respiratory care. 2005;50(9):1209-27.
77. Clark AR, Weers JG, Dhand R. The Confusing World of Dry Powder Inhalers: It Is All About Inspiratory Pressures, Not Inspiratory Flow Rates. J Aerosol Med Pulm Drug Deliv. 2020;33(1):1-11.
78. Frijlink HW, De Boer AH. Dry powder inhalers for pulmonary drug delivery. Expert opinion on drug delivery. 2004;1(1):67-86.

79. Van Holsbeke C, Marshall J, De Backer J, Vos W. Median mass aerodynamic diameter (MMAD) and fine particle fraction (FPF): Influence on lung deposition? European Respiratory Journal. 2014;44(Suppl 58):P912.

80. Ghosh S, Ohar JA, Drummond MB. Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers. J Aerosol Med Pulm Drug Deliv. 2017;30(6):381-7.

81. Dalby RN, Eicher J, Zierenberg B. Development of Respimat(®) Soft Mist™ Inhaler and its clinical utility in respiratory disorders. Medical devices (Auckland, NZ). 2011;4:145-55.

82. Iwanaga T, Tohda Y, Nakamura S, Suga Y. The Respimat(®) Soft Mist Inhaler: Implications of Drug Delivery Characteristics for Patients. Clinical drug investigation. 2019;39(11):1021-30.

83. Hochrainer D, Hölz H, Kreher C, Scaffidi L, Spallek M, Wachtel H. Comparison of the aerosol velocity and spray duration of Respimat Soft Mist inhaler and pressurized metered dose inhalers. Journal of aerosol medicine : the official journal of the International Society for Aerosols in Medicine. 2005;18(3):273-82.

84. Ciciliani AM, Langguth P, Wachtel H. In vitro dose comparison of Respimat(®) inhaler with dry powder inhalers for COPD maintenance therapy. International journal of chronic obstructive pulmonary disease. 2017;12:1565-77.

85. Yeo LY, Friend JR, McIntosh MP, Meeusen ENT, Morton DAV. Ultrasonic nebulization platforms for pulmonary drug delivery. Expert opinion on drug delivery. 2010;7(6):663-79.

86. Dhand R. Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respiratory care. 2002;47(12):1406-16; discussion 16-8.

87. Newman S, Gee-Turner AJJoATR. The Omron MicroAir vibrating mesh technology nebuliser, a 21st century approach to inhalation therapy. 2005;5(4):29.

88. Elhissi AM, Karnam KK, Danesh-Azari MR, Gill HS, Taylor KMJJop, pharmacology. Formulations generated from ethanol-based proliposomes for delivery via medical nebulizers. 2006;58(7):887-94.

89. Ali M. CHAPTER 9 - Pulmonary Drug Delivery. In: Kulkarni VS, editor. Handbook of Non-Invasive Drug Delivery Systems. Boston: William Andrew Publishing; 2010. p. 209-46.

90. Cheng YS. Mechanisms of pharmaceutical aerosol deposition in the respiratory tract. AAPS PharmSciTech. 2014;15(3):630-40.
91. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications. British journal of clinical pharmacology. 2003;56(6):588-99.
92. Darquenne C. Deposition Mechanisms. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2020;33(4):181-5.
93. Finlay WH, Darquenne C. Particle Size Distributions. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2020;33(4):178-80.
94. Farkas Á, Jókay Á, Balásházy I, Füri P, Müller V, Tomisa G, Horváth A. Numerical simulation of emitted particle characteristics and airway deposition distribution of Symbicort(®) Turbuhaler(®) dry powder fixed combination aerosol drug. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2016;93:371-9.
95. Usmani O, Roche N, Wahab E, Israel S, Jenkins M, Trivedi R, Dorinsky P, Aurivillius M. A scintigraphy study of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in patients with moderate-to-very severe chronic obstructive pulmonary disease. Respir Res. 2021;22(1):261.
96. Taylor G, Warren S, Dwivedi S, Sommerville M, Mello L, Orevillo C, Maes A, Martin UJ, Usmani OS. Gamma scintigraphic pulmonary deposition study of glycopyrronium/formoterol metered dose inhaler formulated using co-suspension delivery technology. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2018;111:450-7.
97. Dolovich MB. Radiolabeling Methods. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2022;35(4):227-36.
98. Tomlinson H, Allen M, Corlett S, Chrystyn HJERJ. Comparison of urinary salbutamol 30 minutes post inhalation (USAL) and the methacholine dose to reduce the FEV1 by 20%(PD20) to identify the equivalence of inhaled salbutamol products. 1999;14(Suppl 30):328s.
99. Borgström L, Nilsson M. A method for determination of the absolute pulmonary bioavailability of inhaled drugs: terbutaline. Pharmaceutical research. 1990;7(10):1068-70.

100. Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary beta2-adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered dose-inhaler and modified actuator device. British journal of clinical pharmacology. 1993;36(5):445-50.

101. Chrystyn H. Methods to identify drug deposition in the lungs following inhalation. British journal of clinical pharmacology. 2001;51(4):289-99.

102. Delvadia RR, Longest PW, Byron PR. In vitro tests for aerosol deposition. I: Scaling a physical model of the upper airways to predict drug deposition variation in normal humans. J Aerosol Med Pulm Drug Deliv. 2012;25(1):32-40.

103. Longest PW, Bass K, Dutta R, Rani V, Thomas ML, El-Achwah A, Hindle M. Use of computational fluid dynamics deposition modeling in respiratory drug delivery. Expert opinion on drug delivery. 2019;16(1):7-26.

104. Longest PW, Holbrook LT. In silico models of aerosol delivery to the respiratory tract - development and applications. Advanced drug delivery reviews. 2012;64(4):296-311.

105. Koblinger L, Hofmann WJJoAS. Monte Carlo modeling of aerosol deposition in human lungs. Part I: Simulation of particle transport in a stochastic lung structure. 1990;21(5):661-74.

106. Hofmann W, Koblinger L. Monte Carlo modeling of aerosol deposition in human lungs. Part II: Deposition fractions and their sensitivity to parameter variations. Journal of Aerosol Science. 1990;21(5):675-88.

107. Hofmann W, Koblinger L. Monte Carlo modeling of aerosol deposition in human lungs. Part III: Comparison with experimental data. Journal of Aerosol Science. 1992;23(1):51-63.

108. Erdelyi T, Lazar Z, Odler B, Tamasi L, Müller V. The Repeatability of Inspiration Performance Through Different Inhalers in Patients with Chronic Obstructive Pulmonary Disease and Control Volunteers. Journal of aerosol medicine and pulmonary drug delivery. 2020;33(5):271-81.

109. Erdelyi T, Lazar Z, Farkas Á, Furi P, Nagy A, Müller V. Modeling of pulmonary deposition of agents of open and fixed dose triple combination therapies through two different low-resistance inhalers in COPD: a pilot study. 2023;10.

110. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. The European respiratory journal. 2005;26(2):319-38.
111. Standardized lung function testing. Report working party. Bulletin europeen de physiopathologie respiratoire. 1983;19 Suppl 5:1-95.
112. Kolonics-Farkas AM, Kovats Z, Bohacs A, Odler B, Benke K, Agg B, Szabolcs Z, Müller V. Airway obstruction can be better predicted using Global Lung Function Initiative spirometry reference equations in Marfan syndrome. Physiology international. 2021.
113. Jókay Á, Farkas Á, Füri P, Horváth A, Tomisa G, Balásházy I. Computer modeling of airway deposition distribution of Foster(®) NEXThaler(®) and Seretide(®) Diskus(®) dry powder combination drugs. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2016;88:210-8.
114. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, Knobil K, Willits LR, Yates JC, Jones PW. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax. 2009;64(11):939-43.
115. Sanchis J, Gich I, Pedersen S. Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? Chest. 2016;150(2):394-406.
116. van Boven JFM, Lavorini F, Dekhuijzen PNR, Blasi F, Price DB, Viegi G. Urging Europe to put non-adherence to inhaled respiratory medication higher on the policy agenda: a report from the First European Congress on Adherence to Therapy. The European respiratory journal. 2017;49(5).
117. Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A, Droz-Perroteau C, Lassalle R, Moore N, Girodet PO. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. The European respiratory journal. 2017;49(2).
118. Ding B, Small M, Scheffel G, Holmgren U. Maintenance inhaler preference, attribute importance, and satisfaction in prescribing physicians and patients with asthma, COPD, or asthma-COPD overlap syndrome consulting for routine care. International journal of chronic obstructive pulmonary disease. 2018;13:927-36.

119. Colthorpe P, Voshaar T, Kieckbusch T, Cuoghi E, Jauernig J. Delivery characteristics of a low-resistance dry-powder inhaler used to deliver the long-acting muscarinic antagonist glycopyrronium. Journal of drug assessment. 2013;2(1):11-6.
120. Feldman GJ, Sousa AR, Lipson DA, Tombs L, Barnes N, Riley JH, Patel S, Naya I, Compton C, Alcázar Navarrete B. Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study. Advances in therapy. 2017;34(11):2518-33.
121. Ivancsó I, Böcskei R, Müller V, Tamási L. Extrafine inhaled corticosteroid therapy in the control of asthma. Journal of asthma and allergy. 2013;6:69-80.
122. Haidl P, Heindl S, Siemon K, Bernacka M, Cloes RM. Inhalation device requirements for patients' inhalation maneuvers. Respiratory medicine. 2016;118:65-75.
123. Berlinski A. Assessing New Technologies in Aerosol Medicine: Strengths and Limitations. Respiratory care. 2015;60(6):833-47; discussion 47-9.
124. Mitchell J, Newman S, Chan HK. In vitro and in vivo aspects of cascade impactor tests and inhaler performance: a review. AAPS PharmSciTech. 2007;8(4):E110.
125. Müller V, Gálffy G, Eszes N, Losonczy G, Bizzi A, Nicolini G, Chrystyn H, Tamási L. Asthma control in patients receiving inhaled corticosteroid and long-acting beta2-agonist fixed combinations. A real-life study comparing dry powder inhalers and a pressurized metered dose inhaler extrafine formulation. BMC pulmonary medicine. 2011;11:40.
126. Müller V, Gálffy G, Orosz M, Kováts Z, Odler B, Selroos O, Tamási L. Characteristics of reversible and nonreversible COPD and asthma and COPD overlap syndrome patients: an analysis of salbutamol Easyhaler data. International journal of chronic obstructive pulmonary disease. 2016;11:93-101.
127. Usmani OS, Baldi S, Warren S, Panni I, Girardello L, Rony F, Taylor G, DeBacker W, Georges G. Lung Deposition of Inhaled Extrafine Beclomethasone Dipropionate/Formoterol Fumarate/Glycopyrronium Bromide in Healthy Volunteers and Asthma: The STORM Study. J Aerosol Med Pulm Drug Deliv. 2022;35(4):179-85.
128. EMC. Fostair 100/6 inhalation solution, https://www.medicines.org.uk/emc/product/6318/smpc, Assessed: 09.19.2022.

129. EMC. Spiriva Respimat 2.5 microgram, inhalation solution, https://www.medicines.org.uk/emc/product/407/smpc, Assessed: 09.19.2022.
130. Compendium EM. Trimbow pMDI 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution. 2020.
131. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet (London, England). 2017;389(10082):1919-29.
132. Ierodiakonou D, Sifaki-Pistolla D, Kampouraki M, Poulorinakis I, Papadokostakis P, Gialamas I, Athanasiou P, Bempi V, Lampraki I, Tsiligianni I, Kampouraki M, Ierodiakonou D, Tsiligianni I, Lintovoi E, Karanassos D, Papadokostakis P, Poulorinakis I, Maltezis K, Chorti M, Petrovitsos E, Dimopoulou S, Hamind S, Gialamas I, Athanasiou P, Bempi V, Lampraki I, On behalf of the Greek Ug. Adherence to inhalers and comorbidities in COPD patients. A cross-sectional primary care study from Greece. BMC pulmonary medicine. 2020;20(1):253.
133. Bosnic-Anticevich S, Chrystyn H, Costello RW, Dolovich MB, Fletcher MJ, Lavorini F, Rodríguez-Roisin R, Ryan D, Wan Yau Ming S, Price DB. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. International journal of chronic obstructive pulmonary disease. 2017;12:59-71.
134. Miravitlles M, Soler-Cataluña JJ, Alcázar B, Viejo JL, García-Río F. Factors affecting the selection of an inhaler device for COPD and the ideal device for different patient profiles. Results of EPOCA Delphi consensus. Pulmonary pharmacology & therapeutics. 2018;48:97-103.
135. Price D, Keininger DL, Viswanad B, Gasser M, Walda S, Gutzwiller FS. Factors associated with appropriate inhaler use in patients with COPD - lessons from the REAL survey. International journal of chronic obstructive pulmonary disease. 2018;13:695-702.
136. ERS Handbook of Respiratory Medicine. Palange PRG, editor: The European Respiratory Society; 2019 2019-01-01 00:00:00. 886 p.
137. Sanchis J, Corrigan C, Levy ML, Viejo JL. Inhaler devices - from theory to practice. Respiratory medicine. 2013;107(4):495-502.

138. Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A, Droz-Perroteau C, Lassalle R, Moore N, Girodet P-O. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. European Respiratory Journal. 2017;49(2):1601794.
139. Gálffy G, Mezei G, Németh G, Tamási L, Müller V, Selroos O, Orosz M. Inhaler competence and patient satisfaction with Easyhaler®: results of two real-life multicentre studies in asthma and COPD. Drugs in R&D. 2013;13(3):215-22.
140. Alter P, Orszag J, Wouters EFM, Vogelmeier CF, Jörres RA. Differences in the Measurement of Functional Residual Capacity Between Body Plethysmographs of Two Manufacturers. International journal of chronic obstructive pulmonary disease. 2022;17:1477-82.
141. Baloira A, Abad A, Fuster A, García Rivero JL, García-Sidro P, Márquez-Martín E, Palop M, Soler N, Velasco JL, González-Torralba F. Lung Deposition and Inspiratory Flow Rate in Patients with Chronic Obstructive Pulmonary Disease Using Different Inhalation Devices: A Systematic Literature Review and Expert Opinion. International journal of chronic obstructive pulmonary disease. 2021;16:1021-33.

9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Publications related to the subject of the dissertation

Erdelyi T, Lazar Z, Farkas Á, Furi P, Nagy A, Müller V. Modeling of pulmonary deposition of agents of open and fixed dose triple combination therapies through two different low-resistance inhalers in COPD: a pilot study. FRONTIERS IN MEDICINE 10 Paper: 1065072, 10 p. (2023) (Q1)

Erdélyi T, Lázár Z, Odler B, Tamási L, Müller V. The repeatability of inspiration performance through different inhalers in patients with chronic obstructive pulmonary disease and control volunteers. JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY 33: 5 pp. 271-281. (2020) (Q2)

Müller V, Horváth G, Tamási L, Eszes N, Bohács A, Vincze K, Kováts Zs, Lázár Zs, Odler B, Kornafeld A, Erdélyi T, Somogyi V, Losonczy Gy. Obstruktív tüdőbetegségekben alkalmazott inhalációs gyógyszerek célpontjai: receptorok a légúti felszín sejtjein. MEDICINA THORACALIS (BUDAPEST) 68: 1 pp. 6-12. (2015)

9.2. Publications not related to the subject of the dissertation

Groma V, Kugler Sz, Farkas Á, Füri P, Madas B, Nagy A, Erdélyi T, Horváth A, Müller V, Szántó-Egész R, Micsinai A, Gállfy G, Osán J. Size distribution and relationship of airborne SARS-CoV-2 RNA to indoor aerosol in hospital ward environments. SCIENTIFIC REPORTS 13: 1 Paper: 3566, 11 p. (2023)

Erdélyi T. Inhalációs gyógyszeres terápia. In: Muller V, Bohacs A, Eszes N, Horvath G, Lazar Zs, Losonczy Gy, Tamási L, Varga JT (szerk.) Tüdőgyógyászat zsebkönyv vizsgára készülőknek. Budapest, Magyarország: Semmelweis Kiadó (2022) 295 p. pp. 98-101.

Nagy A, Horváth A, Farkas Á, Füri P, Erdélyi T, Madas BG, Czitrovszky A, Merkely B, Szabó A, Ungvári Z, Müller V. Modeling of nursing care-associated airborne transmission of SARS-CoV-2 in a real-world hospital setting. GEROSCIENCE: OFFICIAL JOURNAL OF THE AMERICAN AGING ASSOCIATION (AGE) 44: 2 pp. 585-595. (2022)

Horváth P, Erdélyi T, Süttő Z. Bronchoszkópia nagy kockázatú betegeknél. ORVOSKÉPZÉS 95: 4 pp. 657-662. (2020)

Csoma B, Bárczi E, Mészáros M, Büdi L, Horváth P, Erdélyi T, Vincze K, Süttő Z, Bíró A, Dombai B, Vámos M, Fekete D, Müller V. Tapasztalatok a járvány kezdetén észlelt első COVID-19 betegek ellátásával kapcsolatban a Semmelweis Egyetem Pulmonológiai Klinikán. MEDICINA THORACALIS (BUDAPEST) 73: 3 pp. 192-195. (2020)

Vámos M, Erdélyi T, Szűcs G, Komlósi Zs, Müller V. A bronchoalveoláris lavage. MEDICINA THORACALIS (BUDAPEST) 73: 2 pp. 134-139. (2020)

Erdélyi T, Nagy A, Vincze K, Tárnoki ÁD, Tárnoki DL, Bitay Z, Kiss A, Müller V. Súlyos asztma és bronchiectasia hátterében álló Williams-Campbell szindróma. MEDICINA THORACALIS (BUDAPEST) 72: 6 pp. 324-326. (2019)

Müller V, Erdélyi T, Nagy A, Tamási L. Metasztatikus és lokálisan kiújult tüdő adenocarcinoma kezelés eredményei docetaxel+nintedanib kombinációval. MEDICINA THORACALIS (BUDAPEST) 72: 3 pp. 164-167. (2019)

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