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Lung deposition of inhaled once-daily long-acting muscarinic antagonists *via* standard jet nebulizer or dry powder inhaler, measured using functional respiratory imaging, in patients with chronic obstructive pulmonary disease

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Abstract

Background: Data for bronchodilator deposition *via* nebulizers and dry powder inhalers (DPIs) in the respiratory tract of patients with chronic obstructive pulmonary disease (COPD) are limited. We used functional respiratory imaging (FRI) to determine deposition patterns for revefenacin solution *via* a PARI LC® Sprint® nebulizer and tiotropium powder *via* HandiHaler® DPI.

Methods: Ten patients with COPD, of whom 9 had severe airflow obstruction, were selected from FLUIDDA's database. The study did not enroll patients. Drug deposition in the extrathoracic and intrathoracic regions, including the central and peripheral airways was simulated by FRI. The percentage of delivered dose and central-to-peripheral (C/P) deposition ratio for nebulizer and DPI were evaluated.

Results: Mean ± standard deviation (SD) age was 64.7 ± 7.1 years, height was 168.8 ± 8.5 cm, and percent predicted forced expiratory volume in 1 s was 40.8 ± 12.3%; 50% of patients were men. At optimal inhalation flow, intrathoracic and peripheral deposition was three-fold higher for revefenacin *via* nebulizer than tiotropium *via* HandiHaler (mean ± SD 34.6 ± 8.53% *versus* 10.9 ± 5.67% and 18.2 ± 4.30% *versus* 5.8 ± 2.73% of delivered dose, respectively). Similar results were observed for suboptimal flow (mean ± SD percentage of revefenacin *versus* tiotropium: intrathoracic, 32.1 ± 8.3% *versus* 15.1 ± 5.9%; peripheral; 16.6 ± 4.1% *versus* 8.4 ± 2.9%). The C/P deposition ratio for nebulizer was similar to DPI (mean ± SD 0.915 ± 0.241 *versus* 0.812 ± 0.249 at optimal; 0.947 ± 0.253 *versus* 0.784 ± 0.219 at suboptimal flow), even though the mass median aerodynamic diameter of revefenacin was higher than tiotropium. C/P deposition ratio for revefenacin decreased after bronchodilation (0.915 ± 0.241 pre-bronchodilation *versus* 0.799 ± 0.192 post-bronchodilation), suggesting progressively better deposition in the peripheral region, assuming bronchodilation occurred during the nebulization process.

Conclusions: These results demonstrate more efficient intrathoracic and peripheral deposition for revefenacin *via* standard jet nebulizer than tiotropium *via* HandiHaler, with similar C/P deposition ratio in patients with COPD. Nebulizers are an efficient alternative to DPIs for bronchodilator administration in patients with COPD.

Keywords: anticholinergic agent, DPI, MDI, nebulizer, peak inspiratory flow

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) depend on bronchodilator treatments for symptom relief and long-term maintenance of quality of life and reduction in exacerbations.[1–6] Bronchodilators are commonly administered using dry powder inhalers (DPIs), pressurized metered-dose inhalers (MDIs), soft-mist inhalers, or nebulizers.[7] Each of these devices has specific characteristics and requires a unique inhalation technique, affecting the regional deposition of medication inside the respiratory tract.[8] The therapeutic effect of an inhaled aerosolized treatment is dependent on the amount of drug deposited within the respiratory tract and its distribution within the lung.[9]

During an acute asthma exacerbation, patients are treated with supplemental oxygen, corticosteroids, and inhaled short-acting beta$_2$-agonists to relieve bronchospasm,[10] which is best accomplished if the drug is delivered to the peripheral airways. However, because of narrowed airways and faster respiratory rate during an exacerbation, most of the drug is deposited in the throat and large airways, resulting in lower efficacy and more side effects.[11] Nebulization and MDIs with a holding chamber are frequently used to overcome this problem.[11] In a systematic review of clinical trials conducted in the emergency room, equivalent community setting, or including in-patients with acute asthma, the method of drug delivery did not show a significant difference in hospital admission rates.[11] Similar studies comparing various modes of inhaled drug delivery in patients with COPD are limited.[12] Patients with COPD are more likely to have challenges using MDI and DPI, including inspiratory muscle weakness, arthritis, dementia, poor inhaler technique, and poor inspiratory flow.[13,14] Nebulizers may be more appropriate for these patients; however, questions remain about drug deposition in the respiratory tract relative to other devices. Therefore, in this study, we aimed to examine the relative deposition of two bronchodilators used to treat COPD administered *via* nebulizer and DPI.

In vivo scintigraphy is the most common technique for assessing lung deposition of inhaled drugs;[15] however, its use is limited by complex procedures for radiolabeling the inhaled drug and patients' exposure to radiation.[16] A number of methods, using mathematical modeling, have been developed as an alternative to scintigraphy to predict how a drug will be delivered and deposited in the airways.[16] Functional respiratory imaging (FRI) is a validated, noninvasive quantification imaging method that provides detailed measurements of the lungs and airways and has been used to quantify drug deposition in the respiratory tract as well as its impact on the overall lung function.[16–21] FRI allows the extraction of patient-specific physiologic data or the respiratory system from medical images.[16,17] The technique uses high-resolution images of patients' lungs and computational fluid dynamics (CFD) to model airflow and measures structural and functional characteristics of the respiratory system. Medical images as input data for FRI can originate from diverse imaging methods, including anatomical imaging techniques such as radiography, computed tomography (CT), cone beam CT, and magnetic resonance imaging, and functional imaging techniques such as ultrasonography, scintigraphy, positron emission tomography, and hyperpolarized gas magnetic resonance imaging.[16,17,22] The most frequently used imaging method for FRI is CT.[17] By combining patient-specific anatomical images of CT scans and functional information from CFD, it is possible to assess how orally inhaled products behave in the airways and lungs of an individual patient.[23]

We used FRI to determine the drug deposition patterns for two anticholinergic agents. Revefenacin inhalation solution was administered *via* a PARI LC® Sprint nebulizer and tiotropium inhalation powder *via* the HandiHaler® DPI. Both anticholinergic agents are indicated for the once-daily maintenance treatment of airflow obstruction in patients with COPD.[24,25]

Methods

Patients

The study did not actively enroll patients, rather 10 representative patients with COPD were selected from the FLUIDDA database. Since 2005, FLUIDDA has conducted several prospective clinical trials in a range of lung diseases, including asthma, COPD, interstitial lung disease, cystic fibrosis, and pulmonary hypertension. Several of these studies included the aim to construct a database of highly accurate lung geometries at inspiration and expiration, to be used for patient-specific flow simulations and deposition assessments. For this study, patients with COPD were selected to have a broad range of forced expiratory volume in 1

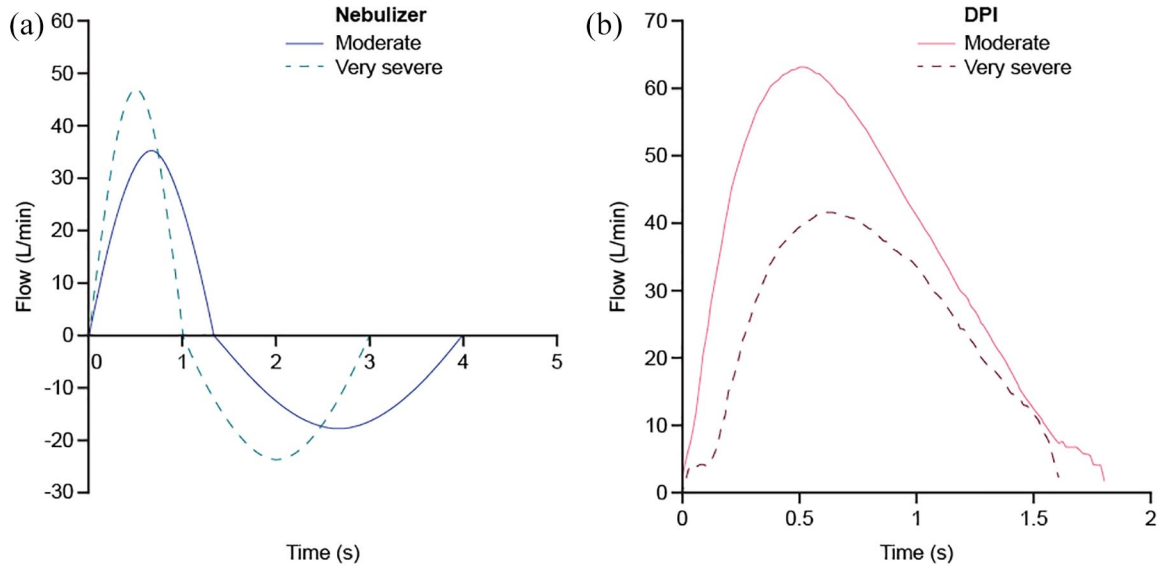

Figure 1. Inhalation profiles for a (a) nebulizer and (b) DPI.
DPI, dry powder inhaler.

s (FEV_1) as well as a balance between genders. Selection was done by a trained individual, taking in to account several factors, including available clinical data, image quality of the lung structures, and overall representation of the disease group. All patients in the database had provided informed consent. Of the 10 patients, 9 had severe airflow obstruction, with FEV_1 less than 50% predicted, and 1 patient had moderate airflow obstruction ($50\% \leqslant FEV_1 < 80\%$ predicted). Because we did not actively enroll patients, no institutional review board approval was obtained for this study.

Inhalation profile, particle characteristics, and simulation strategy

Drug deposition was simulated following inhalation of revefenacin solution 175 µg (Mylan Specialty L.P., a Viatris Company) *via* a PARI LC Sprint nebulizer (PARI GmbH and its affiliates) with a mouthpiece connected to the PARI Trek® S compressor and tiotropium inhalation powder 18 µg *via* HandiHaler DPI (Boehringer Ingelheim Pharma GmbH & Co.).

For both the nebulizer and DPIs, inhalation profiles were evaluated for patients with different airflow obstruction. Deposition patterns were then simulated using inhalation profiles of patients with moderate airflow obstruction (optimal breathing profile) and those with very severe obstruction (suboptimal breathing) to evaluate the effect of airflow obstruction severity on drug deposition profile and observe differences in regional deposition patterns during real-life usage of the therapy (Figure 1). For nebulizer, the inhalation profile characteristics for patients with moderate airflow obstruction included a tidal volume of 550 mL, a respiratory rate of 15 breaths per minute, and inspiratory:expiratory ratio of 1:2,[26] whereas for patients with very severe airflow obstruction the inhalation profile characteristics included a tidal volume of 375 mL, a respiratory rate of 20 breaths per minute, and an inspiratory:expiratory ratio of 1:2.[27,28] For DPIs, the inhalation profile for patients with moderate airflow obstruction was characterized by an inhaled volume of 1.1 L, an inhalation time of 1.8 s, and a mean inhalation flow rate of 35.7 L/min,[29] whereas for patients with very severe COPD it was characterized by an inhaled volume of 0.7 L, an inhalation time of 1.6 s, and a mean inhalation flow rate of 25.8 L/min.[29]

Particle characteristics were assigned during post-processing to ascertain the mass based on the size of the particles inhaled during the stimulation. The mass to size assignment is dependent on the mass median aerodynamic diameter (MMAD), the geometric standard deviation (GSD), the fine particle fraction, and the delivered dose. The description of the particle characteristics was

Table 1. Particle characteristics.

Device	Drug	Flow rate, L/min	MMAD, µm	GSD	DD, µg	FPF 5 µm, %DD
PARI LC Sprint Nebulizer[a]	Revefenacin	15	4.7	2.3	61.9	50.90
HandiHaler[30]	Tiotropium	39 (moderate)	3.2	1.8	10.2	27.45
HandiHaler[31]	Tiotropium	36 (very severe)	3.9	1.8	7.6	23.21[b]

DD, delivered dose; FPF, fine particle fraction; GSD, geometric standard deviation; MMAD, mass median aerodynamic diameter.
[a]Data on file.
[b]FPF for tiotropium administered *via* HandiHaler in patients with very severe airflow obstruction was 4.7 µm.

based on published literature for different devices and optimal and suboptimal breathing profiles (Table 1). Particle MMAD ± GSD was 4.7 ± 2.3 µm for revefenacin solution administered *via* PARI LC Sprint nebulizer at 15 L/min flow rate (data on file). For tiotropium inhalation powder *via* HandiHaler, particle MMAD ± GSD was 3.2 ± 1.8 µm for optimal breathing profile (39 L/min flow rate) and 3.9 ± 1.8 µm for suboptimal breathing profile (36 L/min flow rate).[30,31]

Drug deposition measures

Deposition in the intrathoracic and peripheral airways was measured as the percentage of delivered dose by nebulizer *versus* DPI. The central-to-peripheral (C/P) drug deposition ratio was assessed for revefenacin *via* nebulizer *versus* tiotropium *via* DPI. For revefenacin alone, drug deposition and the C/P ratio were also assessed using a post-bronchodilator lung model (post-bronchodilation scans were taken 4 h after treatment with formoterol to give an indication on how airway geometries can change during bronchodilation), to assess whether this has an influence on the deposition, given nebulized delivery is not instantaneous but rather occurs over a number of minutes during which bronchodilation is likely to have already started.

FRI methodology

The FRI methodology used to evaluate the drug deposition pattern has been described previously[16,17] and includes the following procedures: scanning and three-dimensional modeling of the patient's respiratory tract, determining the inhaler characteristics, determining the inhalation profile for each device, and modeling lung deposition using computational fluid dynamics. The segmentation and three-dimensional model operations were performed in commercially available validated software packages (Mimics 20.0 and 3-Matic 12.0, Materialize nv, Belgium).

FRI lung zones description

To evaluate regional deposition of medication, the patient's respiratory tract was subdivided into multiple zones (Figure 2) and deposition in each of these zones was assessed. The respiratory tract was first divided into the extrathoracic airway, consisting of the mouth and upper airway, and the intrathoracic airway, comprising the trachea and remainder of the airway. The intrathoracic airway was subdivided into the central and peripheral airways. The central airway consisted of the trachea and all airways with diameter >1–2 mm, as far as the 7th–10th generation of dichotomous branching. The peripheral airways included those airways with a diameter <1–2 mm and >10 generations of branching.

Statistical analyses

All statistical analyses were conducted using R version 3.2.5 or higher (R Foundation for Statistical Computing, Vienna, Austria). Drug deposition and the C/P deposition ratio are presented as boxplots showing the median and quartiles with whiskers extending to the most extreme data points, which were no more than 1.5 times the interquartile range from the box. All data points outside this range (outliers) are shown as individual points. Correlation between the C/P drug deposition ratio and FEV_1 and forced vital capacity (FVC) measurements was also evaluated.

Results

Patients

Data from 10 representative patients with COPD were selected from FLUIDDA's database (Table

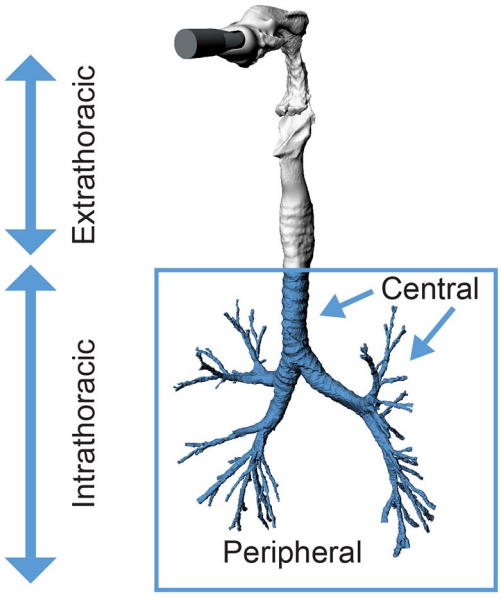

Figure 2. Three-dimensional model of patient's respiratory tract.

Table 2. Patient characteristics.

Patient	Sex	Age (years)	Height (cm)	FEV_1 percent predicted	FEV_1/FVC
001	F	78	171	62	0.53
002	F	51	160	59	0.55
003	M	70	183	45	0.36
004	M	65	171	44	0.39
005	M	63	169	43	0.51
006	F	61	174	37	0.35
007	M	63	161	32	0.32
008	F	60	167	31	0.38
009	M	67	177	29	0.25
010	F	69	155	26	0.24

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

2). Half of the patients were male; the patients' mean age ± standard deviation (SD) was 64.7 ± 7.1 years, and the mean height was 168.8 ± 8.5 cm. Mean percent predicted FEV_1 was 40.8 ± 12.3% and mean FEV_1/FVC was 0.39. Most patients (n = 8) had severe to very severe airflow limitation, with percent predicted FEV_1 <50%; two patients had moderate airflow limitation with percent predicted FEV_1 ⩾50%, but <80%. Two patients (004 and 010) had severe emphysema, which was coupled with a narrow upper airway in patient 010.

Drug deposition measures

The percentage of the total dose delivered was three-fold higher with the nebulizer (revefenacin) than with the DPI (tiotropium) in the intrathoracic and peripheral regions of the respiratory tract for optimal inhalation profile (Figure 3(a) and (c), respectively) and two-fold higher for the suboptimal profile (Figure 3(b) and (d), respectively). For the nebulizer, intrathoracic deposition (% of delivered dose) decreased under suboptimal flow conditions (mean ± SD, 34.628 ± 8.526% to 32.060 ± 8.282%), whereas the converse was true for DPI (mean ± SD, 10.895 ± 5.674% to 15.123 ± 5.893%). A similar pattern was observed for peripheral deposition when comparing optimal with suboptimal flow patterns. The peripheral deposition decreased for the nebulizer under suboptimal flow conditions (mean ± SD, 18.246 ± 4.295% to 16.630 ± 4.095%), whereas an increase in peripheral deposition was observed for the DPI (mean ± SD, 5.843 ± 2.726% to 8.355 ± 2.870%).

The C/P drug deposition ratio for revefenacin administered *via* nebulizer was similar to tiotropium delivered *via* the HandiHaler DPI (mean ± SD, 0.915 ± 0.241 and 0.812 ± 0.249 for optimal flow; 0.947 ± 0.253 and 0.784 ± 0.219 and for suboptimal flow), even though the MMAD for revefenacin was higher than for tiotropium (Figure 4). The C/P deposition ratio for revefenacin *via* nebulizer decreased after bronchodilation, suggesting progressively better deposition in the peripheral region during nebulized delivery (Figure 5). For patients with moderate COPD, the C/P deposition ratio decreased from mean ± SD, 0.915 ± 0.241 pre-bronchodilation to 0.799 ± 0.192 post-bronchodilation and for those with severe COPD, it fell from 0.947 ± 0.253 pre-bronchodilation to 0.827 ± 0.202 post-bronchodilation.

Correlation analysis

A statistically significant negative correlation was observed between the C/P drug deposition ratio and FVC for suboptimal flow when using the nebulizer

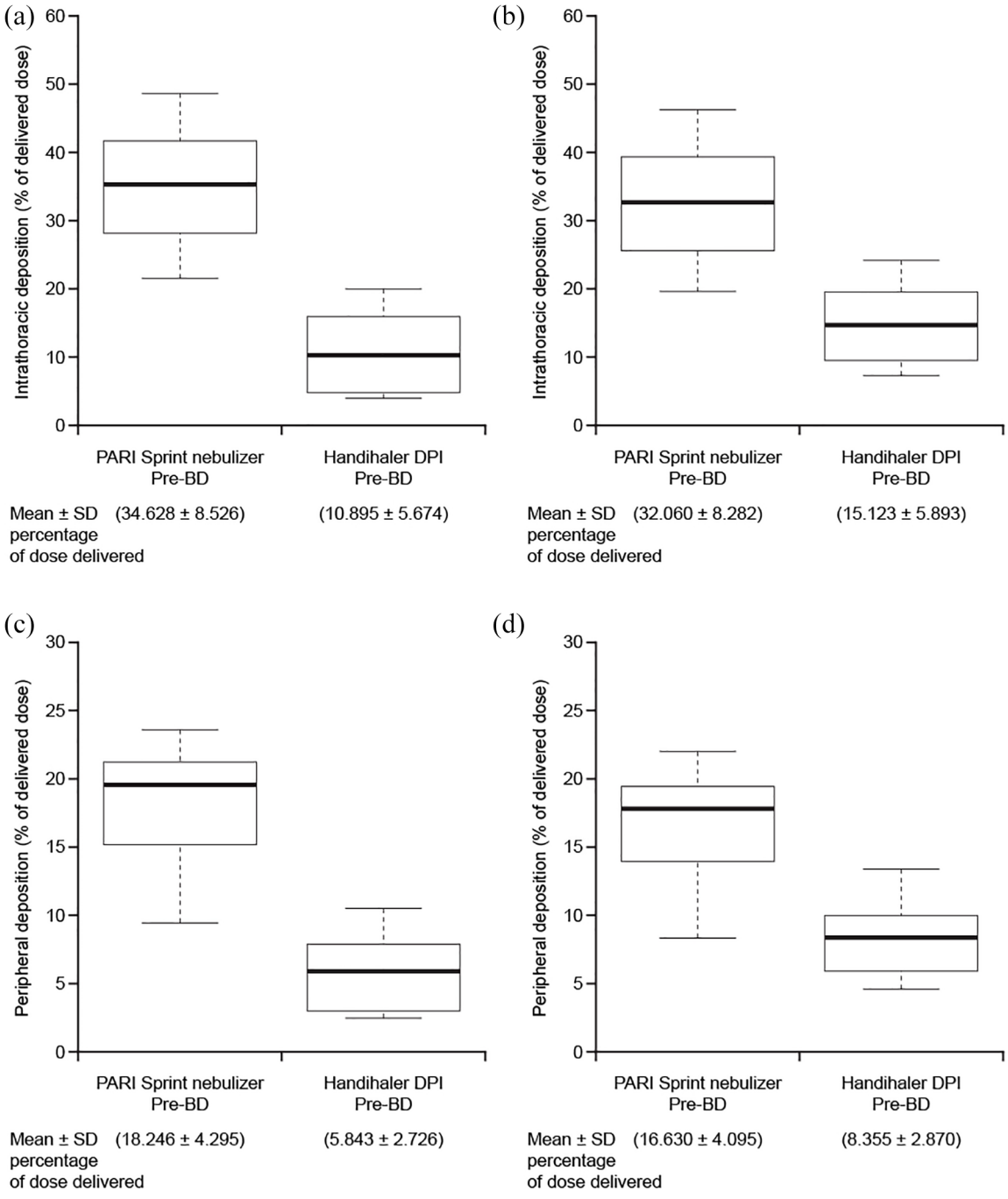

Figure 3. Deposition of revefenacin *via* nebulizer and tiotropium *via* DPI in the respiratory tract. Drug deposition in the (a, b) intrathoracic and (c, d) peripheral regions of the respiratory tract was evaluated under (a, c) optimal and (b, d) suboptimal flow conditions.
BD, bronchodilation; DPI, dry powder inhaler; Neb, nebulizer.

($R^2 = 0.43$, $p = 0.04$; Figure 6(a)) and the DPI ($R^2 = 0.43$, $p = 0.04$; Figure 6(b)). The same trend was observed for FEV_1 [$R^2 = 0.15$, $p = 0.27$ for revefenacin *via* nebulizer (Figure 6(c)); $R^2 = 0.21$, $p = 0.18$ for tiotropium *via* DPI (Figure 6(d))]; however, the correlation was not significant.

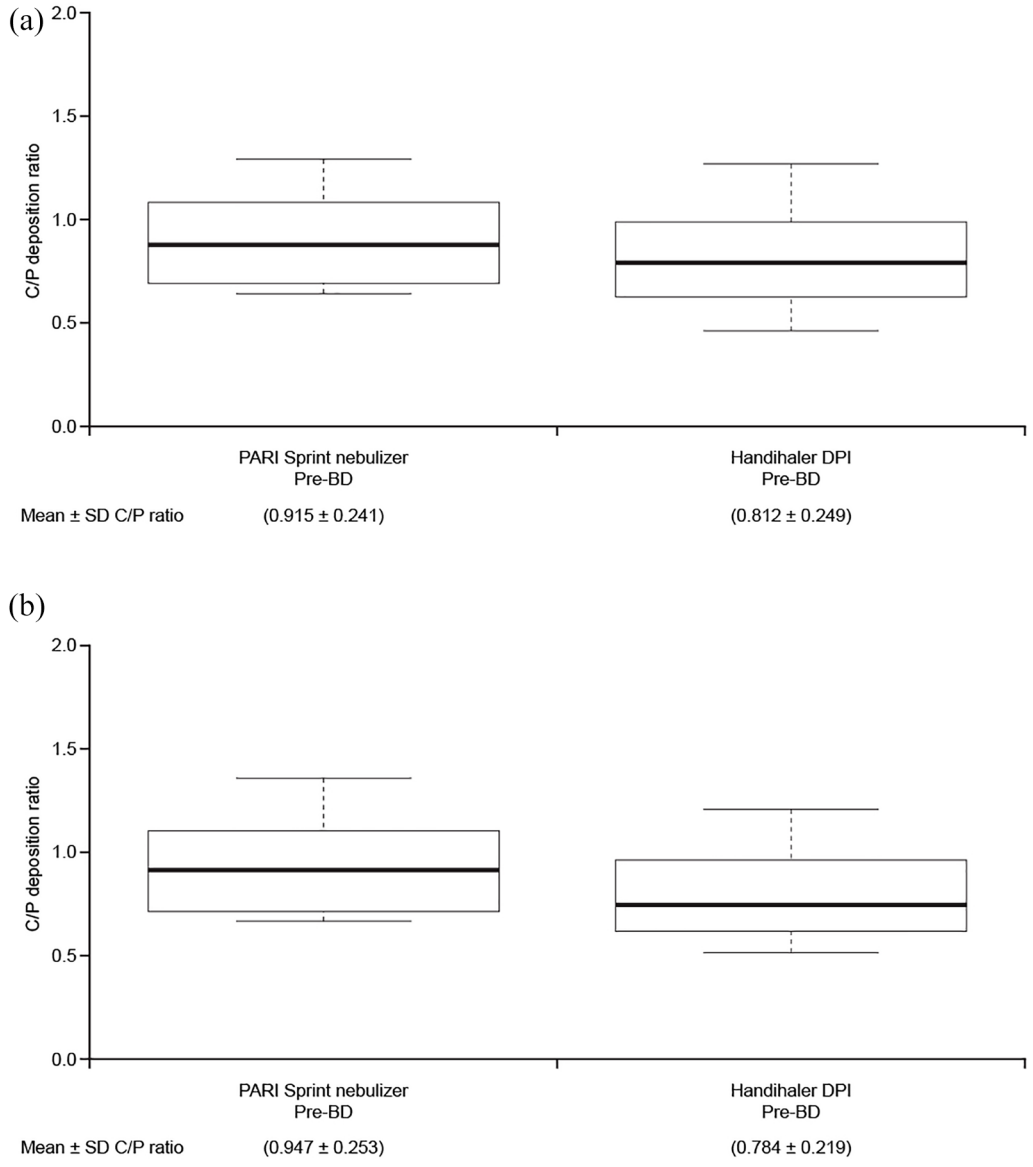

Figure 4. C/P drug deposition ratio of revefenacin *via* a nebulizer and tiotropium *via* a DPI. The drug deposition ratios in C/P regions were evaluated under (a) optimal and (b) suboptimal flow conditions.
BD, bronchodilation; C/P, central-to-peripheral; DPI, dry powder inhaler.

Discussion

In this study using FRI technology to evaluate deposition of inhaled bronchodilators *via* nebulizer versus DPI, intrathoracic and peripheral drug deposition in patients with COPD was more efficient with the nebulizer than the DPI, while the C/P drug deposition ratio was similar across devices despite the higher MMAD for revefenacin *via* nebulizer than tiotropium *via* DPI. Both the intrathoracic and peripheral deposition decreased under suboptimal flow conditions for revefenacin *via* nebulizer, whereas the converse was true for tiotropium *via* DPI. For revefenacin, the initial inhalation flow rate increased more rapidly (Figure 1(a)) for patients with very severe airflow limitation (suboptimal inhalation profile) than for patients with moderate (optimal inhalation profile) airflow limitations, resulting in higher deposition in the extrathoracic region in patients with a suboptimal profile. The HandiHaler device demonstrated increased intrathoracic and peripheral drug deposition in patients with a suboptimal inhalation profile, likely due to consistent

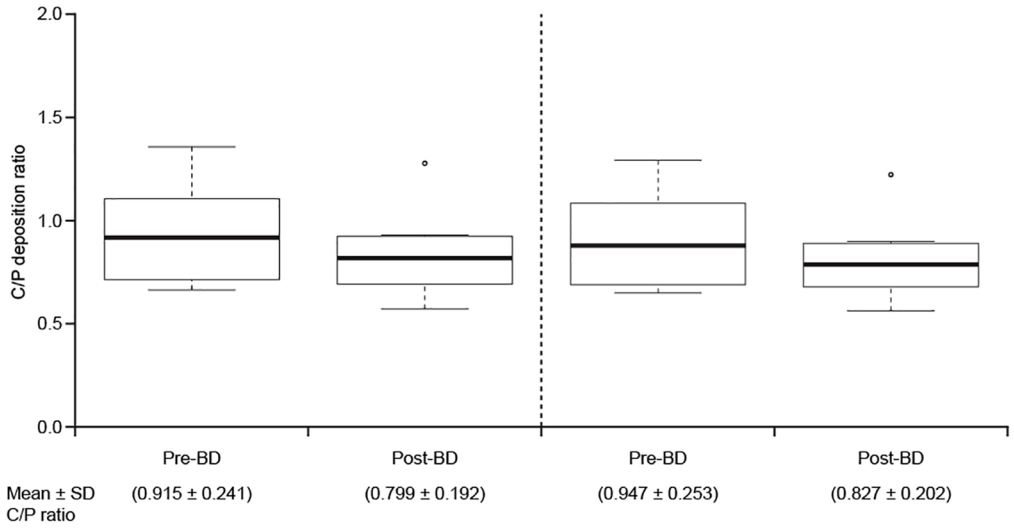

Figure 5. C/P drug deposition ratio for revefenacin in patients with (left) moderate and (right) severe COPD. C/P ratio was evaluated before and after bronchodilation with the nebulizer. Data points outside the post-BD box plots represent outliers.
BD, bronchodilation; C/P, central-to-peripheral.

particle data and a lower flow rate (Figure 1(b)), resulting in less deposition in the upper airways.

The C/P deposition ratio for revefenacin *via* nebulizer showed a decline after bronchodilation, suggesting greater deposition in the peripheral airways. It is possible that during the nebulization process, which takes approximately 6–8 min, there is progressive bronchodilation, resulting in higher peripheral drug deposition and a more homogeneous distribution of the particles overall.

A statistically significant negative correlation was observed between the FVC and C/P deposition ratio for both the nebulizer and DPI. As FVC decreased, more drug particles were deposited in the central airway, suggesting that patients with lower FVC had more difficulty getting delivery of either medication to the distal airways compared with patients with less severe disease. Thus, because of less peripheral deposition of drug particles, patients with low FVC may have less benefit from bronchodilator treatment.

To the best of our knowledge, this is the first time that deposition characteristics of bronchodilators administered *via* two devices have been examined by incorporating patient-specific data. The study results demonstrate that nebulizers, with their unique drug deposition characteristics, are an effective alternative to DPIs for the administration of bronchodilators in patients with COPD. This study provides additional support for FRI as an effective tool to examine the influence of individual biologic and mechanical patient factors on the respiratory system, and on patterns of drug deposition. In addition, it demonstrates an image-based mechanistic and structural rationale for the use of nebulizers in patients with COPD who are unable or not suited to use DPIs.

For treatment with aerosolized medications, the efficacy of an inhaled drug is affected not only by the dose delivered but also where in the respiratory tract it is deposited.[9] The deposition pattern is largely thought to be affected by the particle size.[9] Smaller aerosol particles are thought to be more effective than larger particles in producing bronchodilation because of better penetration and retention in the lungs in the presence of airway narrowing.[32,33] The patient's peak inspiratory flow determines the aerosolized drug particle size and velocity, which in turn affects the probability of drug particle impaction in the oropharynx and larynx.[34] Therefore, for an optimum drug deposition in the lower respiratory tract, fine aerosol particles need to be inhaled at an optimum flow rate. The type of inhalation device used and the drug formulation play an important role in determining the drug aerosol's particle size as well as the inhalation flow rate.[9] In this study, using

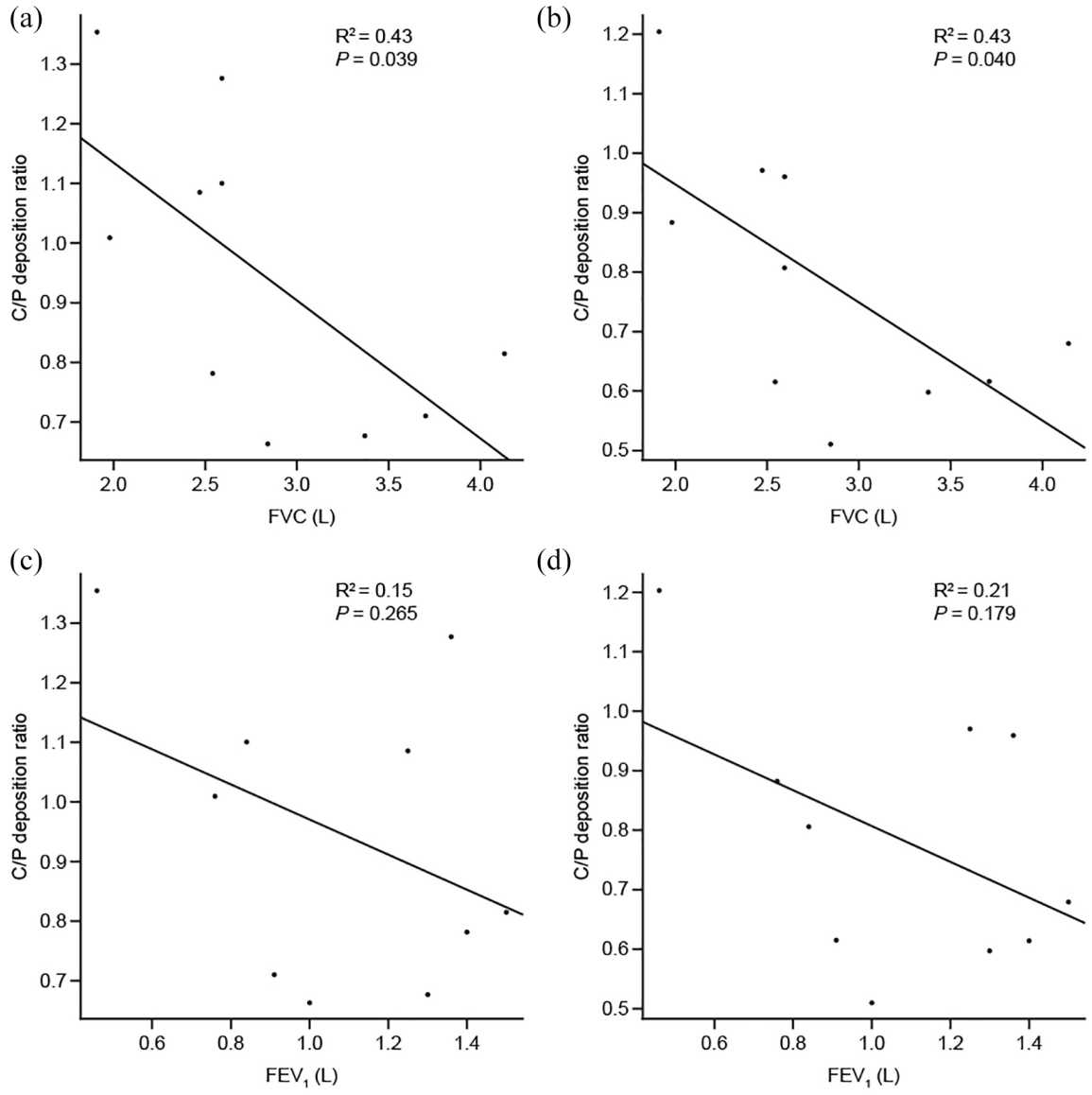

Figure 6. Correlations between the C/P drug deposition ratio and (a, b) FVC and (c, d) FEV_1. Correlations were evaluated for (a, c) revefenacin administered *via* nebulizer and (b, d) tiotropium administered *via* DPI.
C/P, central-to-peripheral; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

patient-specific data, we demonstrated higher intrathoracic and peripheral deposition of revefenacin solution administered *via* a nebulizer compared with tiotropium inhalation powder *via* DPI, despite the higher MMAD for revefenacin than tiotropium. Thus, in addition to the particle size, mode of administration also affects the drug deposition pattern.

The results of this study are limited by the small sample size and the *in silico* nature of the study; however, it included pre- and post-bronchodilation data from actual patients and not just assumed bronchodilation values.

Conclusion

Although DPIs are one of the most frequently prescribed inhalation devices for treating symptoms of COPD, many patients may not be able to use them effectively. Our results show more efficient intrathoracic and peripheral drug deposition from a standard jet nebulizer than HandiHaler DPI and support the use of nebulizers as an

effective alternative to DPIs for the administration of bronchodilators in patients with COPD.

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Author contributions

Glenn D. Crater: Conceptualization; Formal analysis; Methodology; Supervision; Validation; Visualization; Writing – review & editing.

Karmon Johnson: Validation; Visualization; Writing – review & editing.

Jonathan Ward: Conceptualization; Formal analysis; Methodology; Supervision; Validation; Visualization; Writing – review & editing.

Jan De Backer: Conceptualization; Data curation; Formal analysis; Methodology; Software; Supervision; Validation; Visualization; Writing – review & editing.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GDC was an employee of Theravance Biopharma US, Inc. when this study was conducted.

KJ is an employee of Theravance Biopharma US, Inc.

JW is an employee of Mylan Pharma UK, Ltd.

JDB is a shareholder and board members of FLUIDDA NV, a company that has commercialized some of the techniques used in this article.

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Ethics approval and consent to participate

No written informed consent was collected as the study did not actively enroll patients.

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Availability of data and materials

Theravance Biopharma (and its affiliates) will not be sharing individual de-identified participant data or other relevant study documents.

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