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Effects of inhalation procedure on particle behavior and deposition in the airways analyzed by numerical simulation

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ABSTRACT

The therapeutic effect of dry powder inhaler (DPI) formulations can be enhanced by understanding several factors that control the behavior or deposition of inhaled particles in the airways. Computational fluid dynamics (CFD) simulation was performed to predict the behavior and deposition of DPI formulations using a pulmonary model generated on the basis of computed tomography scans of a subject's airway. The effects of inhalation procedures and characteristics, such as flow rate and breath holding, on particle behavior and deposition in the airways were examined. The rate of airflow in the bifurcation area of bronchi was reduced to under 28.3 L/min because, in general, the diameter of the right bronchus is larger than that of the left bronchus in human bronchi. The region of particle deposition differed depending on the rate of airflow. The number of particles deposited in the bronchi decreased upon performing exhalation without breath holding. The results indicated that the turbulence following breath holding promoted particle deposition in the airways. CFD simulation suggested that breath holding is one of the most important factors for enhancing the therapeutic effect of DPI formulations.

1. Introduction

Many patients with lung disease have been treated by the direct pulmonary delivery of drugs [1,2]. Pulmonary administration has drawn substantial attention as a promising new pharmaceutical approach. In fact, it has been shown to improve the systemic delivery and bioavailability of poorly-absorbed drugs as well as the local delivery of anti-asthma drugs because of the large inner surface area (40–100 m^2), thin absorption barrier, and low enzymatic metabolic activity of the lungs [3–6]. Several types of formulations, including nebulizers, pressurized metered-dose inhalers (MDIs), and dry powder inhalers (DPIs), are widely used as tools for the delivery of drugs to the lungs [7]. Over the years, DPI formulations have attracted attention as an alternative to nebulizers or MDI formulations because of their portability and eco-friendliness [8,9].

The effectiveness of DPI formulations can be influenced by several factors, such as age, education, type of inhaler used, and inhalation procedure [10–12]. Specifically, the application of an incorrect inhalation procedure involving an inhaler can lead to treatment failure in patients as a result of an inappropriate amount of drugs being administered in the airways. The procedure for administering DPI formulations using an inhaler has required complicated techniques in patients [13]. However, patients have to perform the correct inhalation procedures to benefit from the therapeutic effect of DPI formulations, which include dose preparation, exhalation, and breath holding. Breath holding, which involves the maintenance of total lung capacity after the inhalation of DPIs, is the lowest acquisition rate of complicated inhalation procedure [14]. Indeed, it is easy for patients to forget breath holding, although this procedure was improved shortly after providing guidance. In this context, it is also necessary to visualize the behavior of particles in the airways to make patients with lung disease sufficiently aware of the importance of breath holding. However, *in vivo* studies of particle behavior and deposition in the actual human lung airway have been limited because of concerns about safety and regulatory constraints. Visualization studies using imaging technology are also limited by resolution and measurements.

To overcome these issues, computer simulation studies including computational fluid dynamics (CFD) have been applied in pulmonary research to assess the behavior and deposition of inhaled particles in the airways [15–17]. CFD is emerging as a powerful computational tool for visualizing and describing particle behavior in dispersed phase flows [18]. CFD analysis has been

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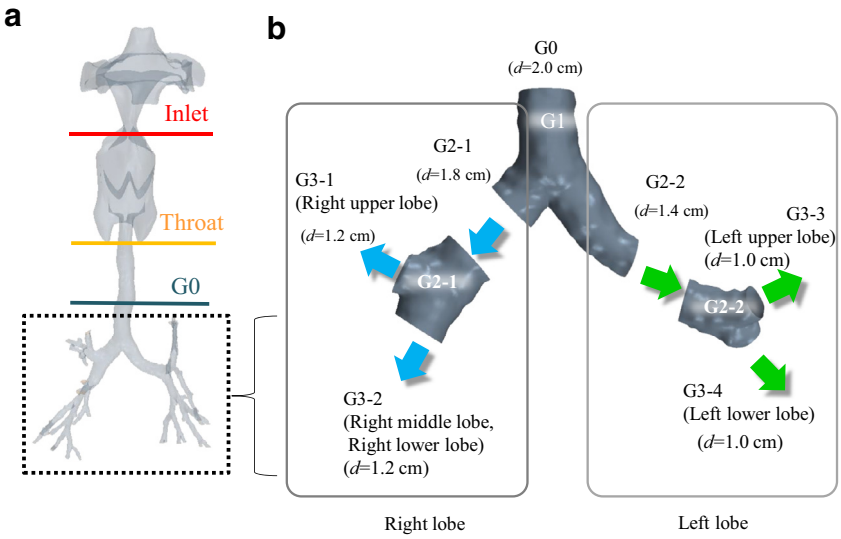

Fig. 1. Realistic human airway model used in computational fluid dynamics simulation. (a) Overview. (b) Generation of geometrical model of the airways.

Table 1
Numerical parameters used in the simulation.

Parameter	Value
Air density [kg/m^3]	1.18
Gas viscosity [Pa•s]	1.82×10^{-5}
Turbulence intensity [-]	0.1
Respiration intensity [m/s]	19.0
Particle diameter of fluticasone (D_{50}) [μm]	5.0
True density of particles [kg/m^3]	1280
Number of particles [-]	4,538,820

performed using pulmonary models based on computed tomography (CT) scan images of a subject's airway [19,20], which have also been used to analyze particle behavior and deposition [21]. Bos et al. [22] demonstrated the relationship between localized lung diseases and inhaled antibiotic concentrations in the airways using 40 patients. These advancements of simulation and CT imaging could lead to the development of individualized medicine for lung disease, delivered by pulmonary administration.

Against this background, the present study aimed to evaluate the effect of inhalation flow and inhalation procedure including breath holding on particle behavior and deposition in a realistic model of the human airway. The effect of inhalation flow rate on the particle behavior and deposition was examined by considering airflows of 28.3 and 60.0 L/min, where the inhalation flow is considered to be represented by uniform inlet velocity. In addition, the effects of the velocity profile, including inhalation, breath holding, and exhalation, on particle behavior and deposition in the airways were investigated. The effect of breath-holding on the particle behavior and deposition in the airways was revealed by CFD analysis.

2. Numerical analysis

2.1. Airway model

A pulmonary model was used, as shown in Fig. 1. The geometry of an actual respiratory system is complicated because of the rough surfaces and moving mucus layers, but we were able to represent this by using a pulmonary model based on CT scan images of a subject's airway, which was supplied by Siemens PLM Software Computational Dynamics K.K. (Kanagawa, Japan) [23]. The model airway featuring the actual geometry was divided into 11 components (mouth, inlet, throat, and generations 0–7) because few dry powder particles reach the deeper lungs. The bronchus model suggested by Weibel [24] has frequently been used for simulating particle behavior or deposition in the pulmonary airway because it mimics the simplicity and reliable symmetricity of the human airway. However, recently, an actual respiratory model has been employed with newly developed medical imaging technology. Several groups have already reported actual pulmonary models based on CT scan images, as mentioned above; more details regarding the CT methods are available in a previous report [25]. Each component of the airway is separated by the bifurcation of the bronchial tubes, as shown in Fig. 1 [26,27]. This airway model included 1,211,676 cells, with the model being meshed entirely with polyhedral control volumes, with particularly high mesh density near the walls [28]. Fluticasone DPI® was chosen as a target product in this study.

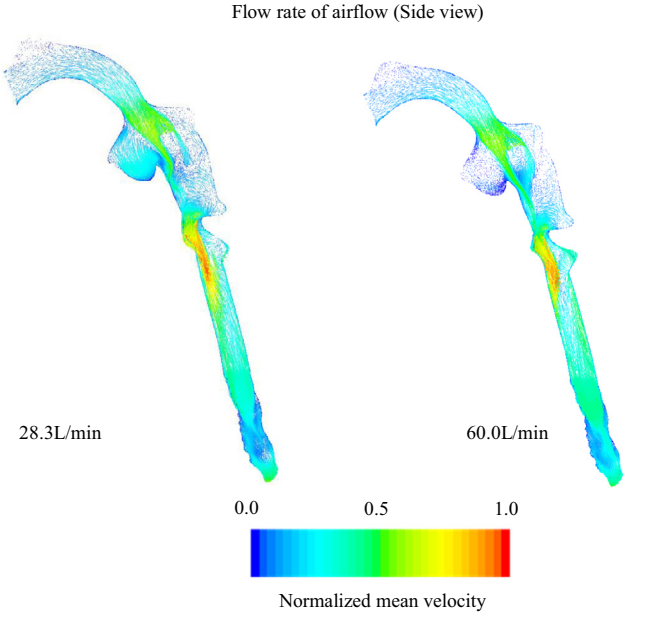

Fig. 2. Difference in velocity vector of airflow in the airways: (a) 28.3 L/min and (b) 60.0 L/min.

2.2. Steady flow simulations

Assuming a dilute phase of inhaled particles in the airways, the effects of particle behavior on the flow field and interactions

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