

Dynamic flow characteristics in normal and asthmatic lungs

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SUMMARY

Complex flow patterns exist within the asymmetric branching airway network in the lungs. These flow patterns are known to become increasingly heterogeneous during disease as a result of various mechanisms such as bronchoconstriction or alterations in lung tissue compliance. Here, we present a coupled model of tissue deformation and network airflow enabling predictions of dynamic flow properties, including temporal flow rate, pressure distribution, and the occurrence of reverse flows. We created two patient-specific airway geometries, one for a healthy subject and one for a severe asthmatic subject, derived using a combination of high-resolution CT data and a volume-filling branching algorithm. In addition, we created virtually constricted airway geometry by reducing the airway radii of the healthy subject model. The flow model was applied to these three different geometries to solve the pressure and flow distribution over a breathing cycle. The differences in wave phase of the flows in parallel airways induced by asymmetric airway geometry and bidirectional interaction between intra-acinar and airway network pressures were small in central airways but were more evident in peripheral airways. The asthmatic model showed elevated ventilation heterogeneity and significant flow disturbance. The reverse flows in the asthmatic model not only altered the local flow characteristics but also affected total lung resistance. The clinical significance of temporal flow disturbance on lung ventilation in normal airway model is obscure. However, increased flow disturbance and ventilation heterogeneity observed in the asthmatic model suggests that reverse flow may be an important factor for asthmatic lung function. Copyright © 2015 John Wiley & Sons, Ltd.

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KEY WORDS: lung ventilation model; airway network; airway constriction; asthma; reverse flow

1. INTRODUCTION

Obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), cause an increase in ventilation heterogeneity, consequently increasing ventilation–perfusion mismatch and leading to impaired gas exchange efficiency. The spatial heterogeneity of ventilation is increased in these diseases by, for example, bronchoconstriction, airway remodeling, or lung hyperinflation because of emphysema. While this heterogeneity has not been fully characterized, it has been investigated via both medical imaging techniques [1, 2] and computational modeling approaches [3]. However, the temporal heterogeneities of ventilation occurring because of structural abnormalities are more difficult to measure and are consequently not well understood.

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In an early modeling study of ventilation, Otis *et al.* introduced a theoretical model of interregional flow between parallel air pathways of a single bifurcation to highlight the occurrence of temporal ventilation heterogeneity [4]. This transient and reverse flow (RF) phenomenon, termed pendelluft, was found to occur predominantly before and after the respiratory phase change because of unequal time constants (a product of resistance and compliance) of the airways. Heterogeneous time constants arise within the airway tree because of differences in branch length, diameter, and resultant airway resistance. Consequent phase difference of the flow waves between separate pathways can result in temporal flow stagnation, increased ventilation heterogeneity, and RF. Previous experimental studies have shown that the limited airflows in COPD patients displayed extended time constants and a significant pendelluft phenomenon [5, 6]. These studies, both modeling and experimental, have emphasized the strong link between airway network geometry and mechanical properties of the tissue governing ventilation distribution.

Three-dimensional (3D) computational fluid dynamic analysis within subject-specific geometries may provide reliable assessment of flow characteristics in large airways [7–9]; however, modeling flow within an entire airway tree remains a major computational challenge. As an alternative approach, recent studies introduced ventilation models within anatomically structured one-dimensional (1D) airway geometry [10, 11]. Swan *et al.* [11] applied a theoretical formula of compliant lung motion [12] to describe the movement of acinar wall and compute the terminal bronchial flow based on lung displacement and local tissue deformation [13]. This allowed the model to predict the topographic distribution of ventilation in upright healthy lungs. However, the acinar flow in their model was determined by transmural pressure; the influence of the pressure gradient within the airway network system was not included. Consequently, the correlation between air pathway resistance and ventilation remained insignificant, while the effect of acinar compliance was dominant. More recently, Ismail *et al.* presented a reduced dimensional flow model comprising a 0D airway tree coupled to a four-element Maxwell model, representing acinar volume changes during breathing [10]. Flow rate, lung resistance, and lobe volume changes were presented for a single healthy subject model and were in good agreement with experimental recordings. The model was used to study the flow characteristics in a breathing cycle, but the existence of dynamic flow phenomenon such as RF was not presented. Moreover, the phase difference in lobe volume changes, which should be found in an asymmetric physiological lung, was not shown in their study.

Here, we introduced a fully coupled computational model of acinar dynamics and an airway network system. The coupled model enabled mutual feedback exchange between the two subsystems to demonstrate the occurrence of RF in anatomically structured airways. The model presented here is the first to simulate dynamic flow, with a focus on RF, in an asthmatic model developed from patient CT data as opposed to constricting a normal model.

2. MATERIALS AND METHODS

2.1. Patient data

CT data at full inspiration from two (one normal and one asthmatic) subjects with similar lung volumes were utilized in this study. Volumetric whole lung CT scans were obtained using a Siemens Sensation 16 scanner at Glenfield Hospital, Leicester, using the following low dose protocol: 16×0.75 -mm collimation, 1.5-mm pitch, 120 kVp, 40 mAs, 0.5-s rotation time, and 500-mm scanning field of view, dose modulation off. The scans were obtained at full inspiration (near total lung capacity, TLC) and at the end of expiration (near functional residual capacity, FRC). Both normal and asthmatic subjects were coached in the breath holding techniques and practiced breath holding, immediately prior to scanning. The asthmatic patient was scanned within 30 min of receiving 400 μ g of salbutamol via a spacer. Images were reconstructed with a slice thickness of 0.75 mm at a 0.5-mm interval using a B35f kernel. Both subjects underwent clinical characterization including clinical history, spirometry, and full pulmonary function tests. The asthmatic subject was characterized as severe persistent with Global Initiative for Asthma classification 5. Informed consent was obtained from both subjects, and the study was approved by the Leicestershire, Northamptonshire and Rutland Research Ethics Committee. Table I shows a summary of the patient information, measured lung volume, and airway tree model data.

Table I. Patients' physiological parameters and airway tree model data.

Subject	Normal	Asthmatic
Gender	F	F
Age at scan	58	51
Height (cm)	160	155
Weight (kg)	75	86
BMI	29.3	35.79
GINA score	0	5
FEV1 (% pred)	94.1	107
FVC (% pred)	107	143
FEV1/FVC (%)	75.27	81
TLC (L)	5.55	5.06
RV/TLC (%)	33.72	38.77
FRC (L)	2.55	2.72
Estimated TV (ml)	430	433
Number of elements	61757	61939
Number of acini	31052	31183
Branch length/diameter	5.42	7.46
Minor child/major child diameter	0.82	0.96

BMI, body mass index; GINA, Global Initiative for Asthma; forced expiratory volume at timed interval of one second (FEV1); FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; TV, tidal volume.

2.2. Geometric models

Surface geometry of the lungs, lobes, and central airways were segmented from the CT images at full inspiration using the commercially available software MIMICS (Materialise, Technologielaan 15, 3001 Leuven, Belgium). Centerlines of the central airways and radii were obtained from the segmented geometries [12], and representative 1D geometry of the smaller airways was grown from the CT terminal branches using a volume-filling algorithm based on that described by Tawhai *et al.* [14]. Radii of the generated airways were assigned based on Horsfield order assuming a diameter ratio of 1.15 between orders. The maximum radii of the generated airways were taken to be the radii at their starting CT terminal branches [15]. The resulting airway geometries (Figure 1a and b) comprised a total of 61,757 and 61,939 line elements in the normal and asthmatic models, respectively. There were 31,052 (normal) and 31,183 (asthmatic) acinar units generated in the airway tree models. The branch generations were numbered using Weibel's generation counting system [16]. Maximum generation numbers in the normal and asthmatic subject models were 25 and 27, respectively. The model was generated into the lung at TLC and was uniformly scaled down to FRC using the scale factor $\sqrt[3]{FRC/TLC}$. The resultant airway models are illustrated in Figure 1.

The most prominent difference between the two airway network models is that the severe asthmatic subject has constricted airways (measured from the CT scan), particularly in generations 5–8 (Figure 1c). Other differences between the models include the impact of the lobar shape and

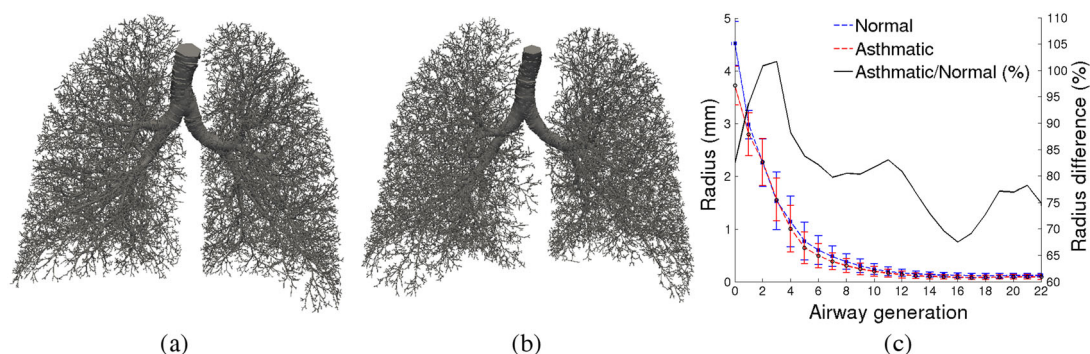


Figure 1. Airway tree models of (a) normal and (b) asthmatic patients and (c) radius versus generation for each model.

volumes on the volume-filling tree and the impact of the patient's lung volumes on determining acinar compliance (Section 2.4). In addition to the normal and asthmatic models, we made an artificial asthmatic model to illustrate the effect of airway constriction only. This model was created such that it would have all the same properties as the normal model apart from having a uniform reduction in airway diameters so that the mean diameter of each generation was equivalent to that in the asthmatic model. To do this, we applied a scaling factor to the airway radii of each generation (derived from the information in Figure 1c) in the normal model.

2.3. Airway network flow model

Dynamics of 1D flow in an airway network system were modeled using electrical components as illustrated in Figure 2. To simplify the model, we assumed the effect of inertial force is insignificant during the normal breathing cycle [10]. Then, the flow in a single airway compartment becomes

$$Q_d = \frac{P - P_d}{R} + \frac{C}{2} \left(\frac{dP}{dt} + \frac{dP_d}{dt} \right), \quad (1)$$

where Q_d is the flow rate in an airway, P and P_d are the nodal pressures, and R and C are the airway resistance and compliance, respectively. Subscript d refers to a daughter branch. According to Ismail *et al.*, the airway wall can be assumed to have a linear elastic compliance of

$$C = \frac{2Lr_{aw}^3}{E_{aw}t_{aw}}, \quad (2)$$

where r_{aw} is the inner radius, L is the length of the airway, E_{aw} is the wall elastance, and t_{aw} is the thickness of the airway [10]. The elastance of the airway wall was assumed to be 3.3 kPa, and the wall thickness (t_{aw}) was assumed to be a function of airway radius (r_{aw}) using the following equation:

$$t_{aw} = k_1 r_{aw}^2 + k_2 r_{aw} + k_3, \quad (3)$$

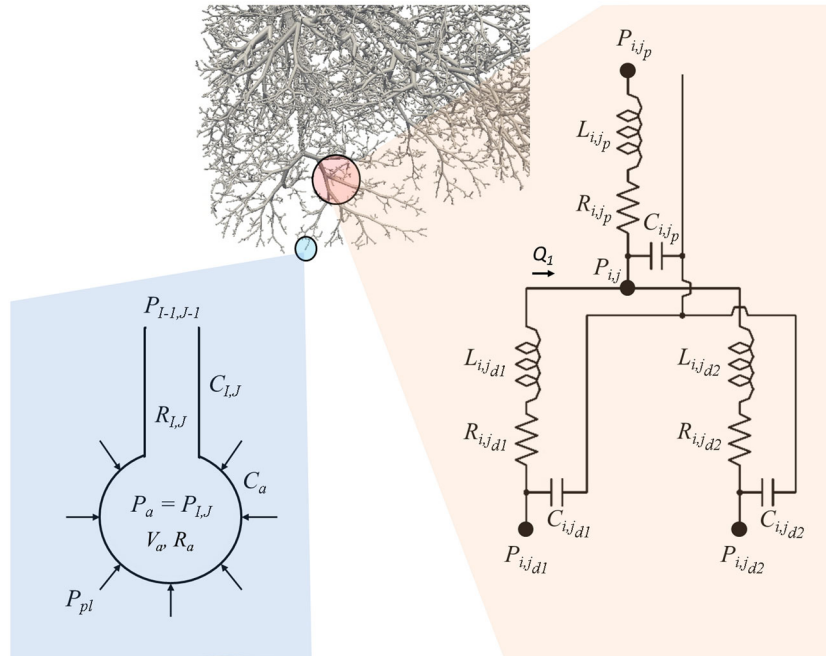


Figure 2. Schematic diagram of the airway network and the acinar dynamics. P_{pl} : pleural pressure, P_a , V_a , R_a , C_a : pressure, volume, resistance and compliance of an acinus. P_{ij} , R_{ij} , C_{ij} , L_{ij} , Q : pressure, resistance, compliance, inductance, flow rate in an airway element.

where $k_1 = -0.0057 \text{ mm}^{-1}$, $k_2 = 0.2096$, and $k_3 = 0.0904 \text{ mm}$. The resistance (R) taking account of a non-parabolic flow profile in airways can be assessed with Poiseuille resistance (R_p) and a correction factor (β) [17].

$$R = R_p \beta \left(Re \frac{D}{L} \right)^{\frac{1}{2}}, \quad (4)$$

where Re is Reynolds number, D (where $D = 2r_{aw}$) and L are the diameter and length of an airway, respectively. The correcting factor ($\beta = 0.162\text{--}0.566$) is a function of generation [18].

Equation (1) includes the pressure in one airway (P) and its daughter airway (P_d) elements. Because one airway element is linked to others and dynamically interacts through the airway network system, pressure and flow in one airway element cannot be calculated in isolation from other airway elements. Thus, we linked the flow equations in the serially or parallelly connected airways and solved the dynamic pressure distribution in an entire airway network system simultaneously. Shown in Equation (5) is the discretized airway network flow equation shown in a matrix format

$$AP = B, \quad (5)$$

$$\begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \\ a_{1,0}^n & a_{1,1}^n & a_{1,2}^n & \cdots & a_{1,M}^n \\ a_{2,0}^n & a_{2,1}^n & a_{2,2}^n & \cdots & a_{2,M}^n \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ a_{M,0}^n & a_{M,1}^n & a_{M,2}^n & \cdots & a_{M,M}^n \end{bmatrix} \begin{bmatrix} P_0^n \\ P_1^n \\ P_2^n \\ \vdots \\ P_M^n \end{bmatrix} = \begin{bmatrix} 0 \\ b_1^n \\ b_2^n \\ \vdots \\ b_M^n \end{bmatrix},$$

where n and M are the time step number and the maximum airway node number, respectively, and P_0^n is the pressure boundary condition ($=0 \text{ Pa}$) at the airway entrance. To compute the instant pressure at a node point, P_m^n , the components in the matrix A become

$$\begin{aligned} a_{m,j_p}^n &= -\left(\frac{1}{R_{j_p}^n} + \frac{C_{j_p}^n}{2\Delta t} \right), \\ a_{m,j_{d1}}^n &= \left(-\frac{1}{R_{j_{d1}}^n} + \frac{C_{j_{d1}}^n}{2\Delta t} \right), \\ a_{m,j_{d2}}^n &= \left(-\frac{1}{R_{j_{d2}}^n} + \frac{C_{j_{d2}}^n}{2\Delta t} \right), \\ a_{m,j}^n &= 0, \quad (\text{if } j \neq j_p, j_{d1}, \text{ or } j_{d2}) \\ b_m^n &= -\frac{1}{2\Delta t} \left\{ C_{j_p}^n (P_{j_p}^{n-1} + P_m^{n-1}) \right. \\ &\quad \left. - C_{j_{d1}}^n (P_m^{n-1} + P_{j_{d1}}^{n-1}) - C_{j_{d2}}^n (P_m^{n-1} + P_{j_{d2}}^{n-1}) \right\}, \end{aligned} \quad (6)$$

where j_p , j_{d1} , and j_{d2} indicate the node numbers of the parent (p) and the daughter branches ($d1$, $d2$) connected to the node point m . At the ends of the terminal bronchioles, the airways are connected to acini. Thus, the pressures in the terminal bronchioles corresponding to the acinar pressure should be computed in a coupled system of airway network and acinar dynamics.

2.4. Acinar dynamics model

In a recent study, dynamic deformation of an acinus was modeled in a damped oscillation system [11]. Assuming isotropic expansion over time t , the equation of acinar motion was formulated as

$$I \frac{d^2 V_a}{dt^2} + R_a \frac{dV_a}{dt} + \frac{V_a}{C_a} = P_a - P_{pl}, \quad (7)$$

where I is the inertance of an acinar unit, V_a is the acinar volume, R_a is the acinar resistance, C_a is the compliance of the acinus, and P_a and P_{pl} are the intra-acinar pressure at the terminal bronchiole and the pleural pressure, respectively, acting on an acinus. The acinar inertance, which has a similar form to lung inertance, is defined as

$$I = \frac{1}{4\pi f C_a}, \quad (8)$$

where f is the resonance frequency of the system during the breathing cycle [19]. Also, assuming isotropic expansion, the Swan model [11] assessed the acinar compliance as

$$C_a = \left[\frac{\xi e^\gamma}{6V_0} \left(\frac{3(3a+b)^2(\lambda^2-1)^2}{\lambda^2} + \frac{(3a+b)(\lambda^2+1)}{\lambda^4} \right) \right]^{-1}, \quad \lambda \geq 1.15, \quad (9)$$

$$C_a = 0.17\xi + 2(\lambda-1)(C^* - 0.17\xi), \quad \lambda < 1.15,$$

where ξ , a , and b are constant coefficients ($\xi=2500$ Pa, $a=0.433$, $b=-0.611$), γ is equal to $\frac{3}{4}(3a+b)(\lambda^2-1)^2$, V_0 is the undeformed acinar volume at residual volume (RV), λ is the isotropic stretch ratio of the acinus from RV, and C^* is the compliance at $\lambda=1.15$. If we assume that the volumetric flow rate, denoted by Q_a , corresponds to the acinar volume change over time (dV_a/dt), then Equation (7) becomes

$$I \frac{d^2 Q_a}{dt^2} + R_a \frac{dQ_a}{dt} + \frac{Q_a}{C_a} = \frac{dP_a}{dt} - \frac{dP_{pl}}{dt}. \quad (10)$$

Here, the acinar flow, Q_a , is substituted by the airway flow equation (Q_d , Equation (1)).

$$Q_a = \frac{P_{\text{term}} - P_a}{R_{\text{term}}} + \frac{C_{\text{term}}}{2} \left(\frac{dP_{\text{term}}}{dt} + \frac{dP_a}{dt} \right), \quad (11)$$

where P_{term} , R_{term} and C_{term} are the pressure, resistance, and compliance of terminal bronchioles used as the airway matrix components in Equation (6). Then, the pressure distribution in both airway (Equation (5)) and acini (Equation (10)) is numerically solved in a fully coupled system. Once the pressure distribution is determined, the flow rate in the airways can be calculated in Equations (1) and (11).

2.5. Simulation conditions

The lung volume measurements (RV/TLC, TLC, and FRC) of the subjects were used to estimate the pre-deformed acinar volume (V_0) at RV and initial stretch ratio (λ) at FRC. We simulate ventilation in the upright posture and apply a linearly decreasing gradient of an initial tissue density ratio in the cranial direction with a 10% random spatial variation factor to elucidate the gravitational influence on the ventilation. The tidal volumes of both subjects are estimated (Table I) assuming 7 ml/kg of estimated body weight (<http://www.manualseb.com/IBW.htm>). A sinusoidal pleural pressure (P_{pl}) wave varying within a physiological range (-890 to -490 Pa, 0.2 Hz) is uniformly imposed

on the acini as a basic input boundary. Then, we revised and scaled each patient's pleural pressure wave to achieve their estimated tidal volume (Normal, -440 to -799 Pa; Artificial asthmatic, -725 to -1317 Pa; and Asthmatic, -995 to -1807 Pa). While the pleural pressure is fluctuating, the pressure at the airway entrance was constant (0 Pa) over the breathing period. The air density and viscosity are assumed to be 1.138 kg/m^3 and $1.9 \times 10^{-5} \text{ Pa} \cdot \text{s}$ at 36°C , respectively. The Reynolds number, resistance, and compliance of each airway element are updated as a function of pressure and flow rates at every time step (Equations (5) and (6)). Once the temporal pressure and flow rate in a breathing cycle are estimated, the amount of RF is assessed in all branches.

3. RESULTS

Ventilation distributions after inspiration to the tidal volumes listed in Table I in the normal and asthmatic models are illustrated in Figure 3 (left). The amount of flow in each acinus (shown as spheres) is represented by the color of the sphere. All airway models reveal heterogeneity in

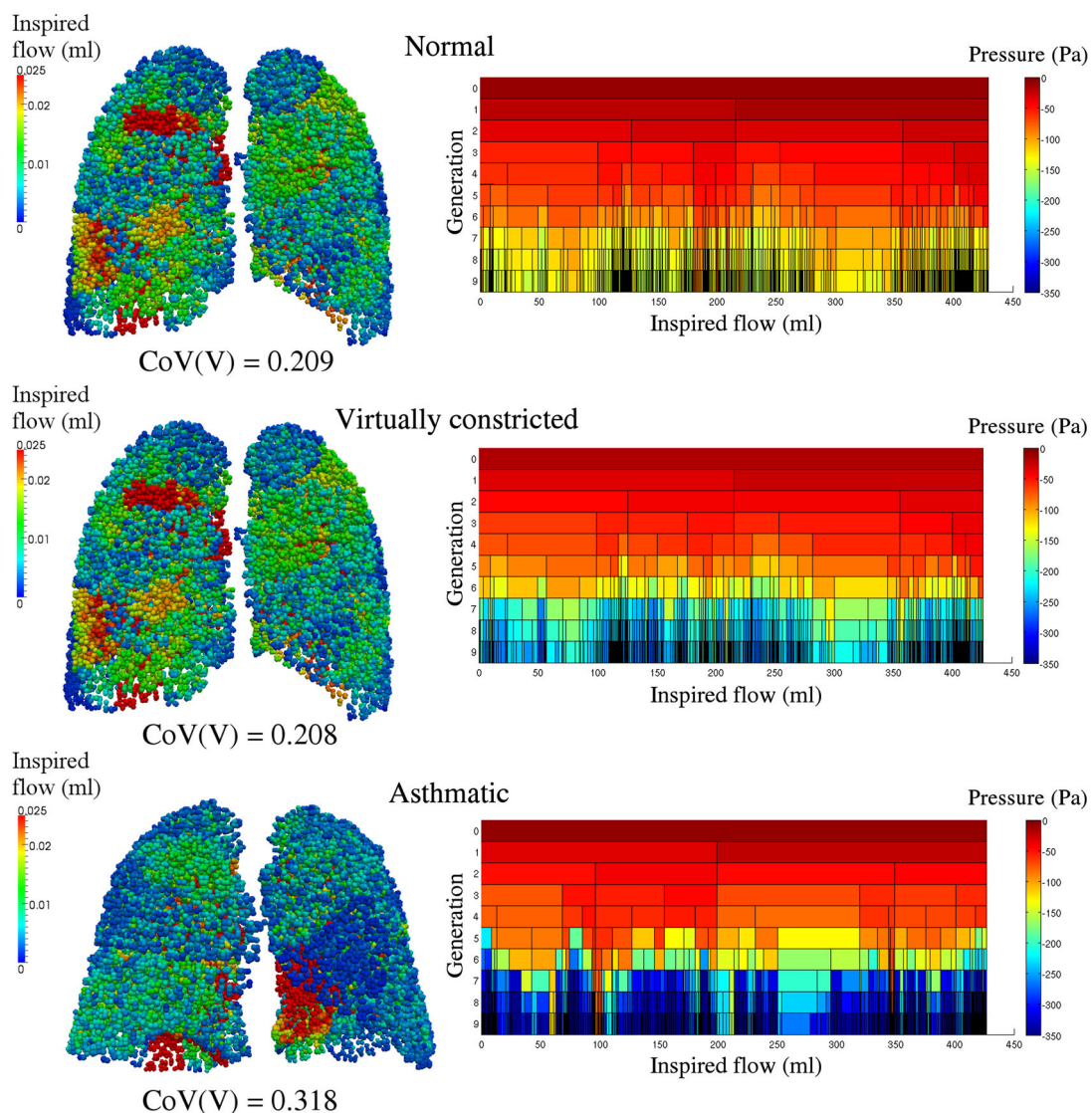


Figure 3. Regional distribution of ventilation in the full conducting airway geometries of normal, virtually constricted, and asthmatic patient airways. Acinar color (left) shows the inspired air volume over a full tidal inhalation. The box plots (right) illustrate the inspired ventilation distribution and the temporal pressure at the peak inhalation for a tidal breath.

ventilation because of their geometrical asymmetry (radii, lengths, and connectivity of the airways). Ventilation heterogeneities in models (over the whole lung) are quantitatively evaluated using the coefficient of variance (equal to the standard deviation divided by the mean). The difference in coefficient of variance between the normal model and the artificial asthmatic models is small, whereas the asthmatic subject model has enhanced ventilation heterogeneity compared with the other models because of the heterogeneous airway constriction.

Figure 3 (right) shows flow and pressure distributions within the first 10 airway generations. The width and color of each box depict inspired flow volume and temporal airway pressure at the peak inhalation, respectively. These plots confirm that the summation of two daughter branch flows is equivalent to their parent branch flow. Flow split ratios from parent to daughter branches in the normal model remain unchanged in the artificial asthmatic model because we applied a uniform constriction factor to all branches in a given generation. However, pressure gradients along air pathways in normal and artificial asthmatic models show a clear difference. There are notable pressure drops between generations 5 and 8 in the artificial asthmatic model where airway radii are reduced by the uniform scaling factor of each generation. The pressure drops in air pathways and the pressure variations within these generations are even more significant in the asthmatic model. The pressure distribution in the parallel airways of generations 4–7 shows more dramatic changes compare with the normal/artificial asthmatic models. Accordingly, some air pathways in the asthmatic model appear to be better ventilated than the other pathways in the normal model. This infers an increased RF due to the imbalanced flows in parallel airways in the asthmatic model.

Figure 4 illustrates the relationship between pressure and flow rate in selected airways (one from each of generations 5 to 7). There is hysteretic behavior of pressure–flow rate curves, which is caused by airway structure and bidirectional flow characteristics in the system. In general, small airways have less flow but bigger pressure fluctuations than large airways. The asthmatic model shows a flattened curve indicating that higher pressures are required to produce the same amount of flow that is induced in the normal subject model. Because the pressure at the tracheal entrance of the model was assumed to be zero, negative airway pressure should correspond with the inspiratory flow (positive flow rate); meanwhile, positive pressure should be with the expiratory flow (negative flow rate). Therefore, the data points in the first (I) and third (III) quadrants of the graph show the existence of RF induced by time constant differences between daughter branches of a bifurcation. The amount of RF increases in both asthmatic models.

Figure 5 depicts the flow rate changes in large (generation 2, left panel) airways as well as in randomly selected smaller (generation 10, right panel) airways. The large airways feeding lower lobes (G2-1 right lower lobe, G2-3 left lower lobe) have bigger flow waves than the airways growing toward the upper lobes (G2-2 left upper lobe, G2-4 right upper lobe) in the normal and artificial asthmatic models. In these models, the phase difference of the flow rate waves is insignificant in large airways. But the difference becomes obvious in the smaller airways of these models. The asthmatic

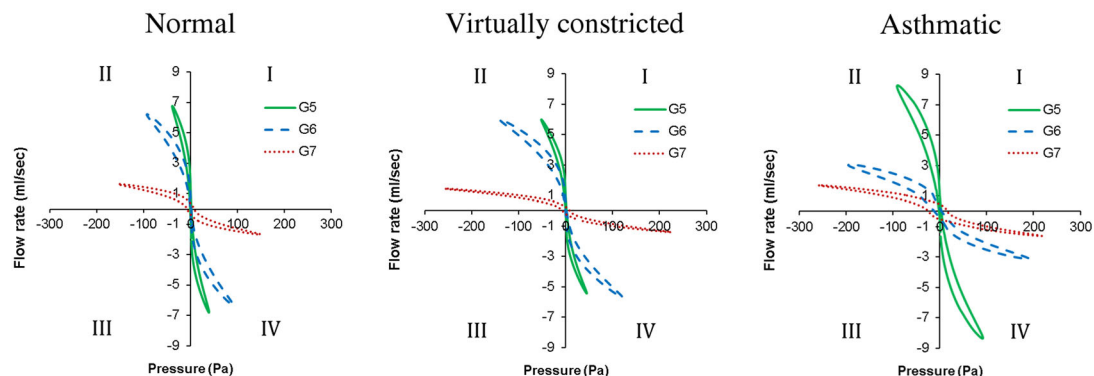


Figure 4. Lobe volume changes (left, summation of acinar volumes only) and pressure versus flow relationship in the selected airways representing typical pressure–flow relationships in generations 5–7 (G5–G7) branches (right).

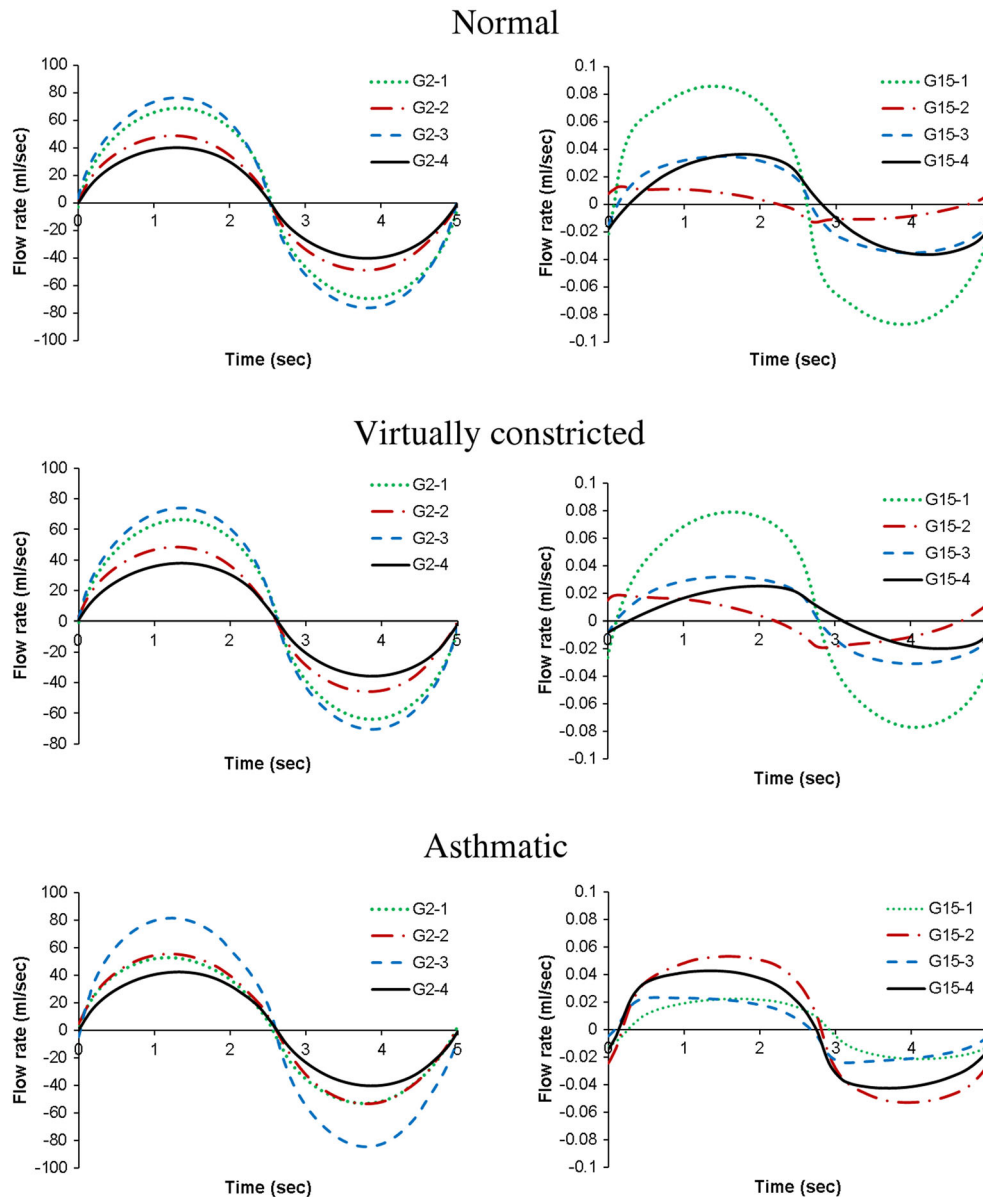


Figure 5. Flow rate variation in sample airways (generations 2 and 10) illustrating temporal flow characteristics in different sized airways.

model displays phase differences in the flow waves even in large airways, and the difference is increased in smaller airways.

Figure 6 demonstrates the rate of the RF occurrence at each airway generation. In all models, the RF occurred during the transient period of expiration and inspiration. The RFs tend to occur more in small airways ($G \geq 15$) than in large airways and more during expiration than during inspiration. The expiratory RF in the normal model is increased in the artificial asthmatic model because of airway narrowing. The asthmatic model has prolonged occurrence of the RF due to the heterogeneous airway constriction pattern.

Figure 7(a) illustrates the variation of total airway resistance as a function of time for a tidal inhalation. The airway resistances of the models increase with increasing flow rates and reach maxima at peak inhalation. Then, they gradually decrease to their minima at the end of inhalation. Airway constriction in the virtual asthmatic model elevates the airway resistance about twofold. The airway resistance is lower in the asthmatic patient model than that in the artificial asthmatic model, but it

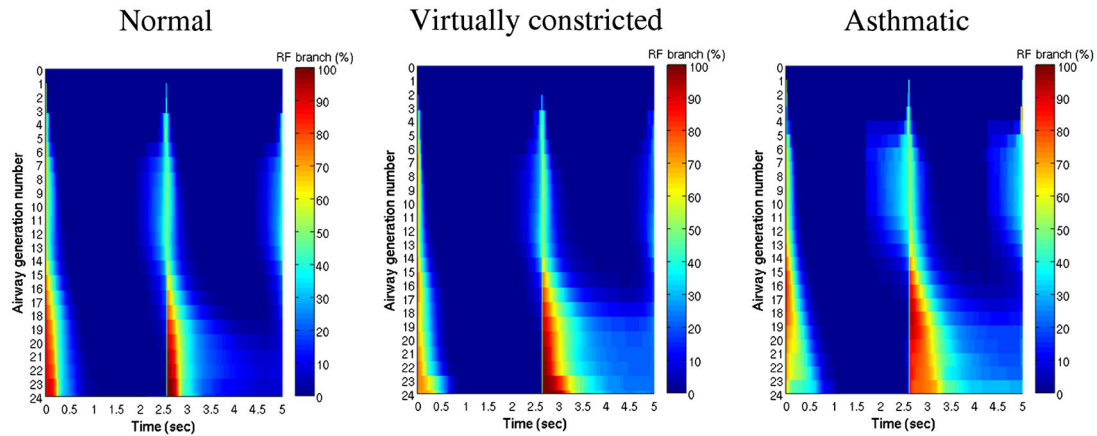


Figure 6. Occurrence of reverse flow (RF) during a breathing cycle. The color maps illustrate the percentage of airway branches within each generation experiencing RF plotted as a function of time. Expiration changes to inspiration at time zero and goes back to expiration at time 2.5 s.

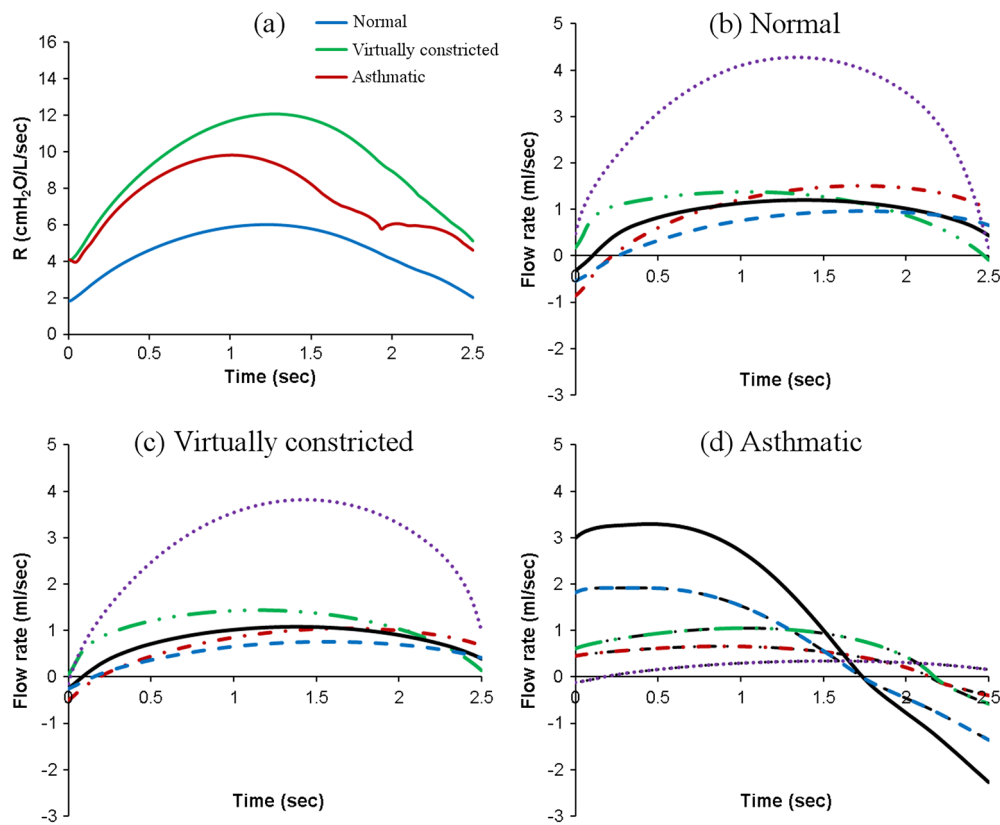


Figure 7. (a) Airway resistance variation during an inhalation. (b)–(d) Flow rates in selected branches of generation 8.

shows irregularities during the deceleration period of inhalation. We believe this is caused by RF in central airways (Figure 6 Asthmatic). To clarify the effect of RF in central airways on the lung resistance, the flow rates in the selected branches of generation 8 are plotted in Figure 7(b)–(d). The phase difference of the flows in the asthmatic model can explain the lung resistance changes. Consequently, we presume that the dynamic flow characteristics such as RF in major airways might affect not only gas exchange rate but also the function of lungs.

4. DISCUSSION

The aggregate behavior of flows in a complete airway network features additional phenomena, which cannot be fully understood by studying flows in a small isolated airway unit [20]. To investigate these phenomena, especially the occurrence of RF, we incorporated the acinar dynamics and the airway network system in a fully coupled flow model. In this coupled model, the static pressure gradient and flow movement in airways were driven by the fluctuating pleural pressure inputs and consequent intra-acinar pressure changes. Here, the intra-acinar pressure was determined not only by the acinar dynamic parameters, such as transmural pressure, tissue elasticity and resistance of acini, but also by the interference from the entire airway network system. Consequently, the two subsystems, acini and airway, exchange feedbacks to reach temporal pressure equilibrium in the model. In the meantime, an acinar unit linked with other acini through the airway network mutually affected the dynamics of the other acinar units. Our model demonstrated the enhanced heterogeneity in the ventilation distribution and the occurrence of RF in asthmatic airways, which has not been investigated in previous ventilation modeling studies of full conducting airway geometry [10, 11].

Airway constriction attenuated air flow and simultaneously decreased acinar compliance via the stretch ratio in Equation (9). During expiration, for example, the flow reduction in a constricted branch may induce pressure decrease at the proximal bifurcation. This bifurcation pressure decrease could lead to a pressure gradient increase in the parallel unconstricted airway and promote flow and acinar volume change. This concurrence of flow reduction and increase between parallel airways agrees with the observations in CT images [21]. In a recent study, the coexistence of bronchoconstriction and bronchodilation of airways was explained by the influence of embedded airways on the behavior of other airways within the airway network [20]. Similarly, our airway network model can demonstrate the consequent reduction of flow in narrowed airways and the increased flow in adjacent airways even though those are not shown here because it is beyond the scope of this study.

The interdependence of acini and airways in our model increased the complexity of flow patterns in the full conducting airway model. As a result, the phase difference of incoming flow waves at a bifurcation caused transient airflow movement between parallel airways, so called RF. The existence of RF (pendelluft) in asymmetric airways has been shown in previous computational and experimental studies [6, 22, 23]. Furthermore, we showed the occurrence of RF was not limited to the peripheral airways. The RF occurred throughout almost the entire airway network including central airways (Figures 5 and 6) during a breathing cycle. There was a similarity in the occurrence of RF (first in large airways and later in small airways) between normal and constricted lung models. This RF disturbs the strong convective flow stream and promotes diffusion and unwanted gas mixing [24]. Consequently, it prolongs gas trapping and lowers the efficiency of ventilation affecting gas exchange and drug delivery. Because anatomic airways are asymmetric by nature, it is no surprise that the flow patterns even in a healthy lung are complex and unstable, although the effect might be tenuous. The RFs in large proximal airways could have a profound effect on ventilation distribution even though they only occurred momentarily at the transition between inspiration and expiration. We found significant RF occurrence in the central airways (Figure 6) in the asthmatic lung and that the RF could be correlated to the total lung resistance (Figure 7). Thus, we predict that the RFs could affect the ventilation distribution, gas exchange, and lung function in the diseased lung.

A constricted airway shows two different effects on the lung function and the ventilation distribution. First, a constriction damps the flow waves, because of increased airway resistance, in serially connected airways; however, we applied scaling factors to the pleural pressure boundaries to recover normal tidal volume in the asthmatic cases. Therefore, the constriction in a large airway feeding numerous distal airways and interfering with a large volume of air flow can profoundly affect lung function. This effect does not cause the difference in wave phase and the flow pattern changes in distal airways of descending generations. The second effect of an airway constriction is disturbing flow patterns and causing an imbalance among parallel airways due to unequal time constants (via airway resistance and acinar compliance). This impacts only on the flow in proximal airways to a constriction and their parallel branches. Hence, a small airway constriction can disturb the flow patterns in a larger area of an airway network. Even though the amount of flow reduction in

a small airway is less significant on its own, the small airways are easily constricted, and the effect of a number of small airways narrowing together can be significant. The effect of multiple small airway constrictions causes chaotic complication of the network airflow patterns including RFs and consequent ventilation impairment. In a previous study investigating airway closure, Venegas *et al.* showed that a sudden closure of a small airway breaking the optimized condition of an airway network system led to a large cluster of airway closures and their catastrophic shift [25]. Winkler and Venegas concluded that the interaction and imbalance between parallel airways was the key mechanism of these self-organized patterns of airway closures [20]. We believe that the catastrophic shift in a small airway closure to the ascending and parallel airways observed in that study might be similar to the constriction effect disturbing flows and causing an imbalance of ventilation between parallel airways in the network system.

Otis *et al.* presented measurements of pulmonary compliance changes of normal and constricted lungs as a function of breathing frequency [4]. For quiet breathing, the compliance of constricted lungs decreased with increasing frequency, while the normal lung compliance remained nearly constant. The changes in compliance of constricted lungs were related to the disproportionate discrepancy between time constants in separate airways. Thus, their results shed light on the existence of substantial flow wave inequalities generating pendelluft in constricted lungs. To explore this further in physiological airway structures, we demonstrated that the occurrence of RF increased in the artificial asthmatic lung model and was even more prominent in the asthmatic model. We presume that the RF can increase as a breathing frequency increase while asthmatic patients trying to recover their normal gas exchange rate. Thus, it may result in an apparent pulmonary compliance decrease associated with the tidal volume reduction in the asthmatic patients.

We did not take into account the existence of parenchyma filling the space between acinar units and the interaction of acini through this media in this study. Consequently, the pressure redistribution through Pores of Kohn by collateral ventilation [26] and the mechanical interaction between adjacent acini through parenchymal tissue [27] were ignored. This could affect the realistic prediction of airway flow characteristics including RF. Moreover, the current study did not include the influence of other physiological alterations such as mucus secretion, airway remodeling, and related tissue property changes, which might be more significant in a severely diseased lung. This remains a topic for further investigation. Because 3D geometry of the full airway network is not practically available, we employed a 1D centerline model of the entire conducting airway tree. The laryngeal jet and secondary flows in the upper airways, which might affect the ventilation distribution of the whole system, were not included in this study. A 3D upper airway flow model fully coupled to a 1D model of the remainder of the airway tree could be used to better assess ventilation in a future study. In addition to the geometric assumption of the 1D model, airway resistance was estimated based on the equation of Pedley *et al.* [17]. In their equation, the pressure loss in an airway tree was assessed using Poiseuille resistance and an energy loss factor at each bifurcation. We assumed that the impact of branch angle on energy loss was negligible. A recent study supporting this assumption showed that the contribution of the branch angle on pressure loss at a bifurcation was insignificant [28]. Finally, the pleural pressure boundary conditions applied within the anatomical model were spatially uniform, although in reality, these may vary throughout the lung. In future studies, these factors should be considered to obtain a better assessment of the diseased lung ventilation.

5. CONCLUSIONS

This study presented a framework of a coupled model incorporating acinar dynamics and airway network flow. The model was applied to physiological airway geometries to simulate the airway pressure and flow variation during a breathing cycle of the normal and asthmatic lungs. The asthmatic lung model revealed high ventilation heterogeneity and profound RF occurrence. The RF occurred mostly in small airways and disturbed local flows to affect gas exchanges. However, the occurrence of RF in the central airways of the asthmatic lung model was notable. It consequently exerted an influence on the lung resistance. This inferred that the dynamic flow characteristics such as RF should be considered as an important factor not only aggravating gas exchanges but also regulating lung function in asthmatic lungs.

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