Simulation of Forced Expiration in a Biophysical Model, With Homogeneous and Clustered Bronchoconstriction

Kerry L. Hedges¹

Auckland Bioengineering Institute,
University of Auckland,
Private Bag 92019,
Auckland 1142,
New Zealand
e-mail: k.hedges@auckland.ac.nz

Merry H. Tawhai

Auckland Bioengineering Institute,
University of Auckland,
Private Bag 92019,
Auckland 1142,
New Zealand
e-mail: m.tawhai@auckland.ac.nz

One limitation of forced spirometry is that it integrates the contribution of the complex and dynamic behavior of all of the airways and tissue of the lung into a single exhaling unit, hence, it is not clear how spirometric measures are affected by local changes to the airways or tissue such as the presence of “ventilation defects.” Here, we adapt a wave-speed limitation model to a spatially distributed and anatomically based airway tree that is embedded within a deformable parenchyma, to simulate forced expiration in 1 s (FEV_1). This provides a model that can be used to assess the consequence of imposed constrictions on FEV_1 . We first show how the model can be parameterized to represent imaging and forced spirometry data from nonasthmatic healthy young adults. We then compare the effect of homogeneous and clustered bronchoconstriction on FEV_1 in six subject-specific models (three male and three female). The model highlights potential sources of normal subject variability in response to agonist challenge, including the interaction between sites of airway constriction and sites of flow limitation at baseline. The results support earlier studies which proposed that the significant constriction of nondefect airways must be present in order to match to clinical measurements of lung function. [DOI: 10.1115/1.4033475]

Keywords: forced expiration, ventilation defects, computational modeling

Introduction

Forced expiration remains the most widely used clinical test in the diagnosis and monitoring of pulmonary disease. The forced expired volume in 1 s (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC) are attractive due to their simplicity and repeatability; however, previous studies have shown poor correlation with morphometry on volumetric imaging for some subjects [1]. One limitation of forced spirometry is that it integrates the contribution of the complex and dynamic behavior of all of the airways and tissue of the lung into a single exhaling unit, hence it is not clear how FEV_1 or FEV_1/FVC are affected by local changes to the airways or tissue. For example, the importance of regional differences in lung structure and function in asthma have been highlighted by recent imaging [1–3] and mathematical modeling studies [4,5] that have suggested “clustering” of airway closure or “ventilation defects.” It is unknown whether the location and magnitude of this clustering is important in interpreting forced expiration.

Developing a deeper understanding of the contribution of clustered bronchoconstriction to forced expiration is limited by the lack of an established structure–function model for the dynamic forced expiratory test, with which the sensitivity of the forced expiration to the structural properties of the airway tree and their inter-relationship with disease location can be tested. Mathematical models have previously been developed to study the relationship between bronchoconstriction and forced expiration. For example, Lambert et al. [6] utilized a wave speed model to investigate flow limitation through a symmetric representation of the airway tree [7]. This single-path model was used to investigate the dimensions of individual airway generations that were required to replicate maximum expiratory flow volume (MEFV) curves for

both healthy and asthmatic lungs. An intrinsic limitation of the single-path model is that all airways in a generation have identical geometry and function, hence the impact of heterogeneity in parallel pathways cannot be studied. Polak and Lutchen [8] used an airway model with regular asymmetry [9] to counter this limitation. The model introduced a level of airway heterogeneity, however due to computational limitations, it was restricted to the analysis of a subset of pathways, and it was not designed to include spatial heterogeneity. Several other model approaches have also been proposed, including a bi-alveolar lung model [10], a bipolar transistor model [11], and a two-element lumped parameter model [12]. A limitation of these previous models is that their geometric simplification precludes their application in studying the effect of regional change to the airways or tissue on forced expiration, or in understanding intersubject variability.

Tgavalekos et al. [13] and Mitchell et al. [14] have previously used structure-based models to represent the spatial distribution and branching geometry of the airway tree, in studies that probed the relationships between regional airway constriction and lung impedance or inert gas washout, respectively. This approach has not previously been used within the context of the forced expiration. Here, we adapt the wave-speed limitation model of Lambert et al. [6] to a spatially distributed and anatomically based airway tree that is embedded within a deformable parenchyma. We first show how the model can be parameterized to individual subject geometry and forced spirometry from nonasthmatic healthy young adults. We then compare the effect of homogeneous and clustered bronchoconstriction on forced expiration in six subjects, to assess intersubject variability in the FEV_1 response to bronchoconstriction.

Methods

The following methods describe a predictive model for forced expiration in geometric models of the human airway tree. The functional model for forced expiration is based on the work of Lambert et al. [6], with modifications to enable its implementation

¹Corresponding author.

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within a branched (not single-path) geometry. To address the potential contribution of intersubject differences in airway tree geometry and driving pressure to FEV₁, models were derived for and parameterized to six normal young adult subjects. The models include intersubject variability in the shape and size of the lungs and airways, the distribution of branches within the lungs, the rate of reduction of diameter with decreasing branch order, and the driving pressure for expiration.

Subject Data and Imaging-Based Model Geometries. Three males and three females were included in the study. Volumetric multidetector row computed tomography (MDCT) imaging and pulmonary function tests (PFTs) were acquired retrospectively from the University of Iowa Comprehensive Lung Imaging Center. Imaging and PFTs of all the subjects were approved by the University of Iowa Institutional Review Board and Radiation Safety Committees, and subjects gave informed consent. The subjects were selected from a study of normal healthy volunteers who had no history of lung disease or smoking, with FEV₁ > 80% predicted, FEV₁/FVC > 70%, normal radiological lung appearance, and all aged less than 40 years. A summary of the relevant subject data is given in Table 1.

The volumetric imaging used in the current study consisted of a spiral scan of the full lung in the supine posture with volume held at 55% of vital capacity (VC). Images were acquired using a Siemens Sensation 64 MDCT scanner, with scan parameters of 120 kV, 100 mA, a pitch of 1.2, slice width 0.6 mm, and slice interval 0.6 mm. The lungs and airways (to a minimum of generation 6 and maximum of generation 10) were segmented from the images using the custom-built software “PASS” (PULMONARY ANALYSIS SOFTWARE SUITE, University of Iowa, Iowa City, IA). The airway segmentations were automatically analyzed using PASS to calculate the centerlines of the airways, location of branch divisions, and airway radii.

Finite element models for the lung and airways were derived to fit segmented data for each subject using the methods described by Tawhai et al. [15]. A finite element model with tricubic Hermite interpolation functions was geometry-fitted to the surface data of each lung. Airway centerlines were converted to a one-dimensional (1D) finite element mesh with a tree-like connectivity, and the image-based radius was associated with each airway element. Additional airways were generated using a volume-filling algorithm [15] to fill the lung volumes with a tree from the trachea to the ~32,000 terminal bronchioles. For the branches that were generated using the volume-filling approach, radii were assigned using a fixed Horsfield diameter ratio (R_{DH}) to define the rate of reduction in diameter with reducing Horsfield order. The R_{DH} was initially set for each subject to give anatomical deadspace as estimated from their height [16].

Model for Flow Limitation. The Lambert et al. [6] model uses wave speed theory [17] to limit the flow of air through elastic airways that undergo dynamic compression during the forced expiration. The pressure gradient along an airway (dP/dx) is defined as

$$\frac{dP}{dx} = \frac{-f(x)}{\left(1 - \frac{U^2}{c^2}\right)} \quad (1)$$

where $f(x)$ is a function that represents the viscous pressure drop along the airway, U is the local velocity, and c is the speed at which disturbances in the flow can propagate upstream (the wave speed). $f(x)$ is described by the empirical expression [18]

$$f(x) = \frac{8\pi\mu\dot{V}}{A^2}(a + b\text{Re}) \quad (2)$$

where μ is the fluid viscosity, $\dot{V}$ is the flow through the airway, Re is the Reynolds number, and a and b are the numerical constants (1.5 and 0.0035, respectively, based on measurements in human airway casts [18]). c^2 in Eq. (1) is defined as

$$c^2 = \frac{A}{\rho(dA/dP)} \quad (3)$$

where A is the airway area and ρ is the gas density. dA/dP is an airway pressure–area relationship given by

$$\alpha = \frac{A}{A_{\max}} = \begin{cases} \alpha_0 \left(1 - P_{tm}/P_1\right)^{-n_1}, & P_{tm} < 0 \\ 1 - (1 - \alpha_0) \left(1 - P_{tm}/P_2\right)^{-n_2}, & P_{tm} \geq 0 \end{cases} \quad (4)$$

where α is the ratio of airway cross-sectional area to maximal cross-sectional area, α_0 is this ratio at zero transmural pressure (P_{tm}), n_1 and n_2 are dimensionless coefficients, and P_1 and P_2 are the equations for the vertical asymptotes of the curves given by

$$P_1 = \alpha_0 \frac{n_1}{\alpha'_0} \quad (5)$$

$$P_2 = -n_2 \frac{(1 - \alpha)}{\alpha'_0} \quad (6)$$

The relationship for dA/dP from Lambert et al. [6] uses values for α , α_0 , n_1 , n_2 , P_1 , and P_2 that were defined for an assumed 16 generation (i.e., generations 0–15) airway tree, α'_0 is the slope of the curve at $P_{tm} = 0$. To generalize the model to an asymmetric tree, the model coefficients were interpolated from generations to Horsfield orders. Coefficients for the highest order were set equal to the values for generation 0, for order 1 were set equal to values for generation 15, and for intermediate orders followed a linear logarithmic decrease with order. The model was found to be insensitive to the equation that was used for interpolating the intermediate orders (results not shown).

The model was further generalized to allow airways within a given order to be initialized to different values (the original model assumed that all airways in a generation had the same dimensions at a given P_{tm}). Scaling was used to allow variation in the airway radii across an order of branching at $P_{tm} = 0$. In conjunction with this, the diameter at a given P_{tm} was related to the initialized diameter by

$$D(P_{tm}) = D(P_{\text{init}}) \frac{\alpha(P_{tm})}{\alpha(P_{\text{init}})} \quad (7)$$

Table 1 Summary of subjects studied

Subject	Sex	Age	FVC (L)	FVC (%P _{red})	FEV ₁ (L)	FEV ₁ (%P _{red})	FEF _{25–75}	PEF (L/s)
F1	F	20	3.43	86	2.94	84	2.89	5.01
F2	F	34	4.37	111	3.51	113	3.39	5.80
F3	F	22	4.46	115	3.60	115	3.44	8.16
M1	M	29	5.97	112	5.00	118	5.34	10.07
M2	M	22	7.35	126	5.22	113	4.01	10.82
M3	M	23	5.37	88	5.24	110	7.42	10.52

where $D(P_{tm})$ is airway diameter at P_{tm} , P_{init} is the estimated P_{tm} during supine imaging, $D(P_{init})$ is the initial airway diameter defined from imaging or by the rate of reduction of diameter with order, $\alpha(P_{tm})$ is the area ratio at P_{tm} , and $\alpha(P_{init})$ is the airway area ratio at P_{init} . P_{tm} at any level of inflation was estimated using a finite deformation soft-tissue elasticity model, as below.

Boundary Conditions: The Driving Pressures for Forced Expiration. During a forced expiration, the elastic recoil pressure of the parenchymal tissue (P_e) and the pressure that is exerted by the respiratory muscles (P_m) are combined to generate a driving pressure, P_d , for the exhalation. Previous models for forced expiration have defined this driving pressure in different ways, e.g., Lambert et al. [6] used increasing values of static recoil pressure to create iso-volume pressure flow curves, and Polak [19] used a time-dependent relationship for the driving pressure that incorporated both P_e and P_m . In the current study, the airway tree is embedded within a deformable model parenchyma, such that simulation of the distribution of parenchymal stress at any volume provides a distribution of P_e . Tissue volume change and P_e were simulated using the finite deformation elasticity model of Tawhai et al. [20]. In brief, this model assumes that the lung tissue is a compressible nonlinearly elastic continuum, with stress and strain related by a strain energy density function (W) given by Fung [21], where

$$W = \frac{\xi}{2} \exp(c_1 J_1^2 + c_2 J_2) \quad (8)$$

J_1 and J_2 are the first and second invariants of the Green–Lagrange strain tensor. The coefficients ξ , c_1 , and c_2 have values 2500 Pa, 0.433, and -0.611 , respectively. The same material law and coefficient values were used for all the subjects, and a theoretical zero stress (reference) state was assumed at 50% of upright functional residual capacity (FRC). This combination of coefficients and assumptions gives a mean P_e of approximately 490 Pa (5 cmH₂O) at FRC. Deformation is simulated with constraints that enforce contact between the lung and a bounding “cavity” shape, such that the lung is free to slide against the cavity boundary. The length of each airway was updated for each deformed configuration, and P_e was calculated at the location of each airway and acinus. The mechanics model was initially computed supine, for validation against imaged tissue density distribution and to initialize the airway compliance model for each subject. That is, the distribution of P_e and the image-based measurements of airway diameter in the supine posture were used to set $D(P_{init})$ and $\alpha(P_{init})$ values for each airway. Subsequent simulations were computed upright.

Flow was not explicitly simulated for the effort-dependent region of the forced expiration, i.e., for $V > V_{PEF}$, where V is the lung volume divided by FVC, and V_{PEF} is V at peak expiratory flow (PEF). In the effort-dependent region of the curve, the flow is not believed to be wave-speed limited: It is dependent largely on the muscle pressure. Any assumption about muscle pressure in this portion of the test would affect the expired volume. To avoid this, flow is only simulated from the PEF onward, however, this requires an estimation of the effort-dependent flow so that the lung volume (therefore elastic recoil) can be reduced accordingly. For the effort-dependent region, a quadratic curve was fitted to pass through the zero flow and PEF points. This allows estimation of the reduction in lung volume that would have occurred prior to PEF, and therefore, the reduction in elastic recoil. The estimated V_{PEF} was between 10% and 16% of FVC for all the subjects.

P_m was defined to have an exponential decay relationship with lung volume in the effort-independent region, with

$$P_m(V) = P_{m(max)} \exp(k_1(V - V_{PEF})^{k_2}) \quad (9)$$

where $P_{m(max)}$ is the maximum muscle pressure, and k_1 and k_2 are numerical constants. k_1 was set proportional to each subject’s

FEF_{25–75} and k_2 was set to 1.9 for all the subjects. P_m was added to the driving pressure from V_{PEF} to the lowest simulated lung volumes, i.e., over the region where flow is limited [22,23].

Subject-Specific Parameterization. Parameters that influence the tissue deformation, airway resistance, and PEF were fitted to imaging and PFT data for each of the six subjects. The mean tissue density was calculated from each subject’s supine imaging, and was scaled to the simulation volumes under the assumption that the tissue weight (including blood) did not change with volume. The model parameters ($P_{m(max)}$, R_{DH}) were fitted to minimize the sum of differences between model and measured results from spirometry for each subject; PEF, FEV₁, and the maximum midexpiratory flow (FEF_{25–75}). This was carried out using a simple grid point technique with the available parameters modified to give a minimal sum of errors between the calculated results and actual spirometry values.

Simulation Methods. The distribution of airway flows and sites of flow limitation were calculated from V_{PEF} to 75% of VC, or for a minimum of 1 s if FEV₁ was greater than 75% VC, using a time interval of 0.05 s. The following steps were used to compute the model solution at any instantaneous lung volume from V_{PEF} onward:

- (1) Total lung flow was initialized to an arbitrary small value (0.01 L s^{−1}), and this was divided uniformly amongst all of the acini (for the first iteration in a time interval).
- (2) The distribution of tissue volume change and P_e was calculated at each airway and acinus for the current lung volume using the finite deformation elasticity model. Pressure boundary conditions at the terminal locations of the tree (the acini) were defined as the summation of the local P_e and P_m . Airway lengths were updated by calculating the location of branch points.
- (3) Beginning with the order 1 airways, a fourth order Runge–Kutta solver with adaptive stepping was used to solve Eq. (1) for the pressure drop along the length of each airway. The pressure at the distal end of higher order airways was approximated as the average of the pressures in the child airways and the flow through the airway was the sum of the two contributing airways (see the Appendix). This pressure was the boundary condition for solution of Eq. (1) in the parent airway of the next order. The solution progressed through the airway tree from the periphery to the trachea.
- (4) Locations of flow limitation were identified (where U was greater than 99% of c). The flows in a limited airway and all of its subtended airways were held fixed for the remainder of the time interval’s computation.
- (5) The total lung flow was incremented by 0.01 L s^{−1}, and this was distributed evenly to all acini that were not peripheral to a flow-limited airway.
- (6) Steps 3–5 were repeated until all acini were peripheral to a flow limited airway. The total expired volume from the model at this point was taken as the flow over the time interval, and the total lung volume (for the finite deformation elasticity model) was decreased by this amount.

Table 2 Percentage errors between measured PFT values and model results

Subject	PEF	FEV ₁	FEF _{25–75}
F1	−2.20	0.85	−1.04
F2	0.34	−6.33	0.23
F3	−5.51	0.79	−1.24
M1	−4.07	−2.26	0.06
M2	−2.5	−0.50	1.36
M3	8.37	−0.15	−0.62

Fig. 1 Illustration of sites of clustered bronchoconstriction in subject F1. Constricted airways are shown in green. (a) six small clusters per lung and (b) two large clusters per lung.

The above procedure was repeated for each incremental time interval, until the total simulation time was greater than 1 s, and the total expired volume was greater than 75% VC.

Following the model parameterization, forced expiration was simulated in the baseline models for comparison of the simulated

FEV₁ to measurements, and to localize the sites of flow limitation and the expiratory flows at which they occurred. The sensitivity of simulated FEV₁ to the degree and localization of airway constriction was then assessed in the six models. The airway cross-sectional area was reduced in increments of 10%, to a maximum of a 50% reduction. Three configurations of constriction were considered: homogeneous, “small” clusters, and “large” clusters. All airways were constricted by the same percentage for the homogeneous constriction. For the two clustered patterns, 28–30% of the terminal bronchioles were included in the clustered (i.e., constricted) regions [24]. Twelve small-sized clusters (six per lung) and four large-sized clusters (two per lung) were selected in each of the six subjects. Clusters were chosen such that they each comprised all of the branches that were distal to a single parent branch (a total of 12 parent branches for small clusters, and four for large clusters), and no clusters spatially adjoined each other. The location and extent of clusters are illustrated in Fig. 1 for a single subject.

Results

Simulation of Subject-Specific Forced Expiration at Baseline. The root mean squared (RMS) error in the predictions of PEF, FEV₁, and FEV_{25–75} were 4.6%, 2.8%, and 0.9%,

Fig. 2 Simulated MEFV (maximum flow against expired volume) curves for normal young adult female (left-hand column) and male (right-hand column) subjects. Individual subject measurements of PEF and FVC are superimposed.

Table 3 Linear regression fits for change in FEV₁ with increasing resistance

Subject	Homogeneous 1	Homogeneous 2	Large clusters	Small clusters
F1	0.262	0.102	0.190	0.263
F2	0.229	0.094	0.261	0.292
F3	0.162	0.078	0.066	0.094
M1	0.196	0.089	0.352	0.443
M2	0.184	0.091	0.293	0.268
M3	0.124	0.083	0.195	0.220

respectively. Errors for all the subjects are listed in Table 2. The most significant error occurs for subject M3 with an over-prediction in PEF of 8.3%. The resulting sum of all errors for this subject still results in a total less than 8% error between the calculated values and actual spirometry values. The total error for all other subjects is below 6%.

Figure 2 shows MEFV curves simulated for all the subjects. Corresponding measurements of PEF and FVC are superimposed on the figures. All of the MEFV curves show the expected characteristic profile for normal healthy lungs, with rapidly increasing maximum flow up to the PEF value (in the effort-dependent portion of the curve) followed by a less rapid decline in flow with

expired volume. Expired volume against time (Fig. 3) illustrates the correspondence between model predictions and measured values of FEV₁ and FEF_{25–75} for the individual subjects.

Intersubject Variability. Homogenous bronchoconstriction was simulated in the six subjects to determine the contribution of individual subject model geometry and parameterization to variability in the simulation of forced expiration. Results are shown in Fig. 4, and listed in Table 3. The sequential data points for each subject in Fig. 4 are for constriction in steps of 10% area, which gives a nonlinear increase in airway resistance. Table 3 lists the percentage change in FEV₁ from baseline for percentage increase in resistance. Values are given separately for 0–20% constriction (with mean $-0.193 \pm 0.049\%/%$), and 20–50% constriction (mean $-0.090 \pm 0.009\%/%$). The percentage change of FEV₁ over the two constriction ranges was significantly different from each other ($p = 0.0017$).

Figure 4(a) shows FEV₁ postconstriction as a percentage of the baseline value, whereas Fig. 4(b) considers FEV₁ postconstriction as a percentage of the subject's predicted FEV₁ from standard reference equations [25]. The dashed horizontal lines in Figs. 4(a) and 4(b) indicate the locations of 20% reduction in FEV₁ from baseline and 80% of predicted, respectively. The former corresponds to the threshold for reduction of FEV₁ (by 20% from

Fig. 3 Simulated results for expired volume against time for normal young adult female (left-hand column) and male (right-hand column) subjects. Individual subject measurements of FEV₁ and FEF_{25–75} are superimposed.

Fig. 4 Airway resistance (Raw) normalized by its baseline value against FEV_1 for homogeneous airway constriction in all the subjects. (a) shows the simulated FEV_1 postconstriction normalized by the FEV_1 simulated at baseline and (b) shows the simulated FEV_1 postconstriction normalized by the subject's predicted value (based on their demographic data).

baseline) that is used during methacholine challenge testing of airway hyper-responsiveness [26]; the latter corresponds to a common diagnostic threshold [27]. The percentage change in FEV_1 from baseline with increasing resistance (Fig. 4(a)) was similar in four of the six subjects. Two of the models for female subjects (F1, F2) were more sensitive than the others to constriction, reaching 20% reduction from baseline at between 20 and 30% homogeneous constriction in comparison to 30–40% constriction for the other subjects. One subject (M3) required 40–50% constriction in order to reach the 20% reduction in FEV_1 from baseline. In Fig. 4(b), at baseline (prior to constriction) all but one subject had a measured (and model) FEV_1 that was greater than the predicted value. The threshold of 80% predicted was reached across a range of 1.23- to 4.0-fold increase from baseline resistance. Subject F1 crossed the threshold with only a 10% airway constriction; subject F2 crossed between a 30 and 40% constriction; subjects F3 and M1 required 40–50% homogeneous constriction while M2 and M3 did not cross the threshold.

Homogeneous and Clustered Bronchoconstriction.

Constriction by 50% within large and small clusters of airways increased the average model resistance by $18.8 \pm 12.9 \text{ kPa m}^{-3} \text{ s}$ ($0.192 \pm 0.131 \text{ cmH}_2\text{O L}^{-1} \text{ s}$) and $17.5 \pm 10.5 \text{ kPa m}^{-3} \text{ s}$ ($0.179 \pm 0.107 \text{ cmH}_2\text{O L}^{-1} \text{ s}$), respectively. The mean reduction in FEV_1 across all the subjects for this resistance range was $4.71 \pm 1.64\%$ for the large clusters, and $5.57 \pm 1.76\%$ for the small clusters. The rate of change of FEV_1 with increasing resistance is listed alongside the homogeneous constriction results in Table 3. The mean decrease in FEV_1 with resistance was $0.226 \pm 0.099\%/%$ and $0.263 \pm 0.113\%/%$ for the large and small clusters, respectively. Neither decrease was statistically different from the mean of the homogeneous constrictions over the 0–20% constriction range ($p = 0.449$ and 0.162 for large and small clusters, respectively). Two subjects (M2 and M3) were more sensitive to clustered than homogeneous bronchoconstriction over the small range of increased resistance that was considered. Two subjects (F1 and M1) responded more strongly to small than large clusters. Subject M2 was slightly more sensitive to large clusters, and subjects F2, F3, and M3 showed very little variation between the types of clustering.

Sites of Flow Limitation. Figure 5 illustrates the sites of flow limitation in each subject for the airway and lung dimensions at the instance of PEF. Each colored cluster shows a flow-limited airway and the airways that are distal to it. The color scale indicates the total lung expiratory flow rate at which flow became limited (i.e., not the flow at the individual airway location). All the subjects show a distinctly individual flow limitation map: there is

no discernable regional pattern in the location of sites of flow limitation. The range of lung expiratory flows over which the airways became flow limited was less than 3.5 L s^{-1} for all but one subject (subject M1 had a range of 5.7 L s^{-1}). Note that Fig. 5 illustrates the sites of flow limitation at only a single time point in the simulation. Results for other time points are not shown, however, the progression of the solution to lower lung volumes resulted in a general trend of peripheral movement of flow limitation sites, with smaller regions of the airway tree limited at lower volumes.

Discussion

We have presented a method for parameterizing a simulation model of the dynamic forced expiration test to imaging and PFT data from individuals. The method allows forward simulation of FEV_1 in spatially distributed models of the airway tree, for comparing the response to controlled bronchoconstriction across models that represent a range of healthy individuals. Here, we have used a set of six models to simulate the FEV_1 and resistance response to uniform and clustered decrease in airway cross-sectional area as a proxy for asthmatic bronchoconstriction.

Parameterizing the Model to Individual Subjects. The current model builds on the work of Lambert et al. [6] These authors used a single path (inherently symmetric) model of the conducting airways, and an inverse approach to optimize the longitudinal distribution of airway constrictions that would allow their simulations to replicate measured values of FEV_1 . We used a similar approach in the current study to inversely parameterize a set of models to baseline measurements of lung function, and then we performed forward simulations. A close approximation to PEF as an optimization target was achieved (RMS 0.27%) by fitting the rate of reduction of diameter with order (R_{DH}) and the peak muscle driving pressure ($P_{m(max)}$), however error in the prediction of FEF_{25-75} was considerably larger (RMS 6.19%). FEV_1 is directly dependent on the rate of exhalation over the first second, which is indicated by the PEF and FEF_{25-75} . Prediction of baseline FEV_1 had RMS error of 1.76% as a result. While the error in this prediction is relatively small, the larger error for FEF_{25-75} indicates that the rate of exhalation between 25% and 75% of FVC was not represented as well. FEF_{25-75} is the estimated average forced expiratory flow between 25% and 75% of FVC, calculated using a straight line approximation. As shown in Fig. 3, the expiratory flow is not constant over this range, meaning that a close approximation to FEF_{25-75} does not necessarily translate to an accurate prediction of FEV_1 .

A unique parameterization cannot be guaranteed using our approach of iteratively modifying the model parameters; however,

by initializing the model to physiologically reasonable values the optimization does reach a valid local minima. Optimization of the model parameters was kept minimal by assuming that all the subjects had identical tissue and airway elastic properties. This assumption is reasonable for healthy young subjects, but would need to be re-addressed if the same analysis was used for older subjects, or for subjects in whom air trapping contributes significantly to the effective stiffness of the lung tissue.

For the parameterized models presented here, the shape of the subjects' MEFV curves remained consistent throughout all manipulations of the models (i.e., for all bronchoconstriction scenarios). That is, there was no change in shape of an individual subject's curve (results not shown). This possibly indicates a role of underlying branching tree geometry in determining the characteristic shape; alternatively, it simply indicates that the rate of decrease of expired flow is not sufficiently sensitive to bronchoconstriction

Fig. 5 Calculated sites of flow limitation in all the subjects at PEF. Clusters of same colored airways indicate regions that are distal to a flow limited airway. The color scale indicates the trachea (whole lung) flow at which the limited airway reached its maximum flow.

Fig. 6 Illustration of effect of variation in pressure at the bifurcations. Solid line shows results using average pressure at each bifurcation in airway tree. Dashed lines show results for ten solutions carried out using pressure values randomly chosen between maximum and minimum pressure entering each bifurcation.

(when using the assumptions that are built in to the current model) to be visually apparent on our results.

One possible extension of this model would be to parameterize a set of generic models that represent different characteristic MEFV shapes. That is, once a sufficient understanding of the interdependent mechanisms that determine the MEFV curve was known, it could then be possible to relate this to particular parameterizations of the model, and relate this to clinically relevant information (e.g., airway tree size and rate of diameter reduction, location of bronchoconstriction, muscle strength). That is, there is potential for advancing this approach as an adjunct tool for diagnostic testing, however, the current model is not yet sufficient for this purpose, as it is highly likely that airway compliance and airway closure will both be important for representing MEFV curve shapes that are characteristic of pathologies.

Intersubject Variability in Sensitivity to Bronchoconstriction. Imposing idealized homogeneous constrictions on the six models allows us to probe the influence of intersubject variability in baseline airway geometry on sensitivity to bronchoconstriction. The percentage increase in resistance from baseline across all six models was quite similar at each level of constriction, however, the rate of change of FEV_1 with increasing resistance was variable. The decrease in FEV_1 was most rapid over the initial constriction (from 0 to 20% area constriction), and was also significantly more variable between subjects within this range than for the 20–50% area constrictions. The two subjects with the greatest decrease in FEV_1 with initial constriction were female. All of the male models behaved similarly with respect to their baseline resistance, and one female model (F3) had similar response to the males. The constriction simulations can be considered as approximating an idealized inhaled methacholine challenge (i.e., with uniform deposition and lumen area reduction that is linearly proportional to dose). The range of increase in resistance was larger than would be considered in a methacholine challenge study: American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines limit the increase in resistance from baseline to only 200%, whereas the model study was extended to approximately 400% of baseline. The greater sensitivity of subjects F1 and F2 is reflected in these two models reaching a 20% reduction in FEV_1 before resistance increased to 200% of baseline; the other four subjects required a much larger percentage increase in resistance to reach this threshold (Fig. 4(a)).

Clustered Versus Homogeneous Bronchoconstriction. Ventilation defects have been observed to be consistent in their location and size [1]. Costella et al. [3] reported a strong

correlation between specific airway resistance and the ventilation defect percentage (VDP) in asthmatics, and de Lange et al. [1] reported an increasing size of ventilation defects with an increasing severity of asthma. One possible interpretation of these data is that VDP size *influences* the airway resistance; alternatively, a large VDP is *symptomatic* of a lung with higher resistance. Our simulation results support the latter interpretation, which is consistent with conclusions from previous modeling studies [13,14]. In Costella et al. [3], the mean VDP was 9.2% postmethacholine challenge and the mean decrease in FEV_1 was $15 \pm 9\%$. In the current study even with a reduction of airway cross-sectional area by 50% within 28–30% of the model airway tree, the reduction in predicted FEV_1 was only $4.71 \pm 1.64\%$ for the large defects, and $5.57 \pm 1.76\%$ for the small defects. The ventilation defects are therefore not sufficient by themselves to reduce FEV_1 in the simulation model by the level seen in Costella et al. [3]. Consistent with the modeling studies of Tgavalekos et al. [13] and Mitchell et al. [14], this suggests that constriction of the nondefect airways is an important characteristic of asthma.

The rate of decrease of FEV_1 with increased airway constriction was similar for homogeneous constriction (in the range of 0–20% constriction) and clustered constriction, when considering the average values across the six subjects. However, the variability in response to clustering was larger than for homogeneous constriction, and some individual subjects showed a distinctly stronger response to one or the other type of constriction. For example, subject M2 had twice the rate of reduction of FEV_1 with increasing resistance for large clusters than for homogeneous constriction. Whether clustered constriction increases the rate of reduction of FEV_1 in comparison to homogeneous constriction depends on the baseline sites of flow limitation in the individual model. Superimposing constriction on airways that are flow limited early in the baseline expiration has a minor effect on FEV_1 in comparison to constricting airways that would have reached relatively high flows before becoming flow limited. As illustrated in Fig. 5, there is no easily discernible pattern in the spatial distribution of the sites of flow limitation, and the sites move location during the course of the expiration. Ventilation defects that are the result of incompletely closed airways therefore potentially contribute to intersubject variability in the relationship between FEV_1 and airway resistance.

Model Limitations. Complete airway closure was not considered in the model. The airways followed the pressure–area relationship defined by Lambert et al. [6], without any mechanism for sudden closure of airways, or “bistability” [4]. Healthy young subjects probably have minimal closure of airways during their forced expiration [28], whereas airway closure is believed to contribute to the “scooped” appearance of the MEFV curves in asthmatics [29]. Including airway closure in this model could improve its fit to FEF_{25-75} at baseline, and would potentially predict less contribution of clustered constricted regions to the forced expiration if they closed early in the expiration. Lack of an airway closure model has consequence for a second limitation, which is that the simulations were terminated at FEV_1 or 75%VC, so FVC was not predicted for any subject. Linear extension of the MEFV curves (i.e., with the same rate of decrease of flow with volume as at 1 s) would give variable accuracy for the prediction of FVC. For example, F1, F2, and M3 would be closely predicted, whereas F3, M1, and M2 would be under-predicted by the model. For the model to be able to simulate FVC, it would need to include a chest wall that limited the minimum volume of the lung, as well as an appropriate model for airway closure.

The proportion of airways in the clustered constricted regions was fixed at 28–30%. Reported values for VDP are variable. We chose a proportion that was consistent with air trapping in a quantitative analysis of 60 severe asthmatics [24]. Ideally, the proportion and location of constricted airways would correspond to imaged ventilation defects, however in the current study we used

data from nonasthmatics and therefore had to impose arbitrary defects.

This was a cohort of healthy young adults therefore the specific compliance of the lung tissue model was assumed to be the same for all the subjects. The model made no attempt to account for changes in tissue elasticity that could have occurred secondary to persistent bronchoconstriction, such as increased elasticity in regions that have abnormally low fluctuation in distending pressures. This could introduce further differences between the behavior of the homogenous and clustered bronchoconstriction models, however, there is currently not sufficient data in the literature to guide this aspect of the model.

Conclusion

We have presented an extension of the Lambert et al. [6] model for simulating forced expiration, and show that it can be parameterized to individual subjects using a relatively straightforward approach. This provides a model that can be used to assess the consequence of imposed constrictions or interventions on the forced expiration. The model predicts intersubject variability in the rate of reduction of FEV₁ with increasing airway resistance. The results highlight potential sources of normal subject variability in response to agonist challenge, including the interaction between sites of airway constriction and sites of flow limitation in the baseline state. The model supports earlier studies that proposed significant constriction of nondefect airways must be present in order to match clinical measurements of lung function.

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Nomenclature

c	= wave speed
dP/dx	= pressure gradient along an airway
$D(P_{tm})$	= airway diameter at P_{tm}
$D(P_{init})$	= airway diameter during supine imaging
FVC	= forced vital capacity
$f(x)$	= viscous pressure drop along an airway
FEF ₂₅₋₇₅	= midexpiratory flow (between 25 and 75% of FVC)
FEV ₁	= forced expired volume in 1 s
J_1, J_2	= first and second invariants of the Green–Lagrange strain tensor
MDCT	= multidetector row computed tomography
MEFV	= maximum expiratory flow volume curve
n_1, n_2	= dimensionless coefficients
PEF	= peak expiratory flow
PFT	= pulmonary function test
P_d	= driving pressure
P_e	= elastic recoil pressure
P_m	= applied muscle pressure
$P_{m(max)}$	= maximum applied muscle pressure
P_{tm}	= transmural pressure
R _{DH}	= Horsfield diameter ratio
u	= local velocity
sVC	= vital capacity
V_{pef}	= volume of lung at peak expiratory flow
$\dot{V}$	= flow through an airway
Re	= Reynolds number
P_1, P_2	= vertical asymptotes for pressure, in the airway compliance relationship
W	= strain energy density function

α = ratio of cross-sectional airway area to maximal airway area

α_0 = airway area ratio at $P_{tm} = 0$

μ = fluid viscosity

ζ, c_1, c_2 = material law coefficients

1D = one-dimensional

Appendix

Effect of Pressure Estimation at Bifurcations. The fluid dynamics generated by conjoining flows at a bifurcation are extremely complex. Pedley [30] provides a review of the foundation experimental studies that still provide the basis of our understanding of flow and pressure drop in branching tubes. Schroter and Sudlow [31] performed flow visualization experiments using plexiglass tubes, of flow through sequences of bifurcations. Their observations showed secondary flows generated downstream of the bifurcation which did not dissipate before the next bifurcation. They concluded that the flow entering a bifurcation from a parent branch cannot be assumed to be unidirectional laminar flow; and that the flows throughout the airway tree should be expected to be disturbed (but still laminar). Simplification to represent the effect of this complex flow is required in order for the model to be solvable over an anatomically structured airway geometry, to allow investigation into regional effects on the forced expiration manoeuvre. To this end, the pressure downstream of each bifurcation was assumed to be the average of the two pressures entering the bifurcation.

The effect of this assumption was tested by varying the pressure at each bifurcation, to somewhere between the maximum and minimum pressures entering the bifurcation. This simulates the effect of pressure fluctuations that would be expected in the disturbed flows downstream of each bifurcation. Simulation of this effect was carried out using a random number generator to vary the downstream pressure between the maximum and minimum upstream pressures at each bifurcation (that is, the maximum and minimum pressures that could reasonably be expected within the disturbed flow). Ten solutions were obtained using this technique and the results are shown in Fig. 6.

The RMS errors between the benchmarked solution that was presented in the “Results” section and the ten solutions considered here are 6.48%, 1.99%, and 3.34% for PEF, FEV₁, and FEF₂₅₋₇₅, respectively. The largest variation occurred in the solution for PEF, with PEF reducing from benchmark for all of the ten random pressure solutions. Given the small potential variation in the solution results, and the computational time required to obtain multiple solutions, benchmarking was carried out using the assumption of average pressures downstream of each bifurcation.

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