Modeling the Effect on Forced Expiration of the Interaction Between Loss of Terminal Bronchioles and Decline in Tissue Elastic Recoil with Age and/or COPD

K.L. Hedges[1], D.M. Vasilescu[2], J.C. Hogg[2], M.H. Tawhai[1]
1. Auckland Bioengineering Institute, The University of Auckland, New Zealand.
2. The Center for Heart Lung Innovation, The University of British Columbia, Vancouver, Canada

Background

Conducting airways <2mm in diameter account for only about 20% of total air flow resistance in the normal lung, however these same airways become the major site of obstruction in COPD(1). Furthermore, using a combination of clinical multi-detector computed tomography (MDCT) and micro-CT it has been shown that narrowing and loss of terminal bronchioles contributes to peripheral resistance in COPD(2). Due to the age-related prevalence of COPD, here we use a structure-based mathematical model to study how FEV_1 changes in response to loss of terminal bronchioles in combination with age-related decline in lung tissue elastic recoil.

Methods

- 6 normal healthy subjects (3 M, 3 F). Table 1 shows a subject summary.
- Structure-based lung and airway models from MDCT(3) (See Figure 1).
- Finite deformation elasticity for tissue displacement and elastic recoil(4).
- Airway tree embedded in model lung tissue.
- Wave-speed model(5) to predict maximum flow at all lung volumes.
- Viscous pressure drop using relationship developed by Collins et al.(6).
- Airway compliance determined using Lambert's model(5).
- Model initiated at total lung capacity (TLC) from which a forced expiration for 1 second (FEV_1) was simulated (time interval 0.05s).
- 'Ageing' of lung simulated by: 1. decreasing lung tissue elastic recoil, and 2. removing terminal bronchioles.
- Baseline model generated for one healthy 63 year old male. Subject extrapolated to other ages that were studied here.

Subject	Age	Height (m)	FVC (L)	P_{ef} (L/s)	FEV_1 (L)	FEF_{25-75}
F1	20	1.63	3.43	5.01	2.94	2.89
F2	34	1.68	4.37	5.80	3.51	3.39
F3	22	1.6	4.46	8.16	3.60	3.44
M1	29	1.77	5.97	10.07	5.00	5.34
M2	22	1.82	7.35	10.82	5.22	4.01
M3	23	1.87	5.37	10.52	5.24	7.42

Table 1. *Subject summary. 3 male and 3 female subjects with no prior respiratory disease, no parenchymal abnormalities on volumetric CT, FEV_1 > 80% predicted, and FEV_1/FVC > 70%. FVC == forced vital capacity; P_{ef} == peak expiratory flow; FEV_1 == forced expired volume in one second; FEF_{25-75} == expiration between 25 to 75% of FVC*

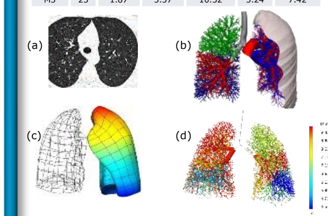

Figure 1. *Biophysical model to simulate forced expiration. (a,b) Structure-based model from volumetric CT. (c) Simulating tissue expansion to TLC, and forced reduction in volume. (d) Sites of flow limitation in subject M1, from wave speed limitation and tissue elasticity models.*

Forced expiration in the baseline model

- Figure 2 shows baseline model results for subject M1 along with measurements from pulmonary function tests.
- Parameterisation of the baseline model by fitting peak muscle (driving) pressure and rate of decrease of airway diameter with decreasing order.
- Variation between measurements and computational results for all six subjects are: FEV_1 2.4 ± 1.2 % ,FEF_{25-75} 4.3 ± 1.8%, P_{ef} 0.3 ± 0.3%

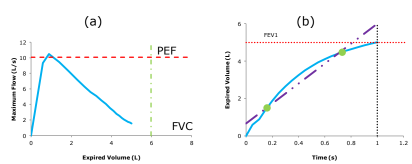

Figure 2. *Baseline model results illustrated for subject M1. (a) Simulated maximal expiratory flow volume curve (blue), and measured peak expiratory flow (P_{ef}, red) and forced vital capacity (FVC, green). (b) Expired volume against time, to illustrate measured FEF_{25-75} (purple) and FEV_1 (red), and location of model data points for FEF_{25-75} calculation.*

Loss of tissue elastic recoil

- Figure 3 shows model prediction of decrease in FEV_1 with 'age' as a % of FEV_1 calculated at 25 years for each subject (males green, females blue).
- Lung tissue compliance by decade identical for all subjects. Muscle pressure and airway dimensions parameterised to baseline young data.
- Loss of tissue elastic recoil in the model results in decreased FEV_1 and increased inter-subject variability.
- The models are in concordance with the literature, including an – on average – more rapid decline in FEV_1 with age in females.

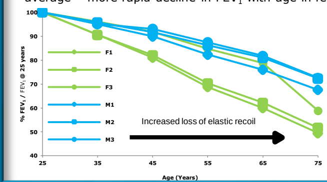

Figure 3. Decline in FEV_1 predicted from 25 to 75 years, where 'age' is simulated as a loss of tissue elastic recoil only. Results are shown as a percentage of FEV_1 at 25 years of age. Male subjects shown in green, females in blue.

Removing terminal bronchioles

- Figure 4 shows the effect on predicted FEV_1 of removing terminal bronchioles in two subjects. Airways removed 20% at a time, by removing every n^{th} airway from the model. i.e. approximately homogeneously.
- Also shown (horizontal lines) are measured FEV_1, FEV_1 predicted from reference equations, and 80% predicted at 25 years of age.
- Note that in F1 the measured FEV_1 was < predicted; removal of only 20% terminal bronchioles was sufficient to decrease FEV_1 below 80% predicted.
- In M2 a loss of 80% of the terminal bronchioles was required in order to reach the 80% predicted FEV_1 threshold.

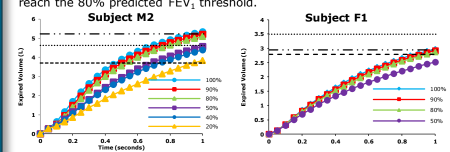

Figure 4. *Decline in model simulated FEV_1 with removal of terminal bronchioles in (a) subject F1 and (b) subject M2. The key lists the proportion of terminal bronchioles remaining in the model. Horizontal lines are shown for measured FEV_1 (— · · —), FEV_1 predicted from reference equations (………), and 80% of predicted FEV_1 (— — –).*

Loss of elastic recoil & terminal bronchioles

- Figure 5 compares two causes of FEV_1 decline.
- Removing 50% of the terminal airways without a change in elastic recoil from the 25 years value (green) decreases FEV_1 by < 20%.
- Decreasing elastic recoil to the 75 years value without removing terminal airways decreases the FEV_1 more in females than males (blue). Results show more subject variability.
- Removing 50% of terminal airways from the model with 75 years elastic recoil decreased FEV_1 by 10-20%, with largest decrease in males.

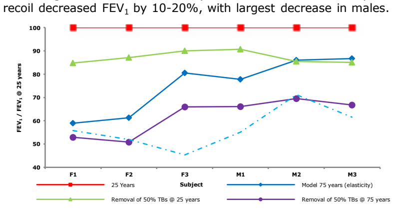

Figure 5. *Comparison of: change in FEV_1 (with respect to its value at age 25 years) due to loss of elastic recoil to the 75 years level (blue), loss of terminal bronchioles from the 25 years lung (green), loss of terminal bronchioles from the 75 years lung (purple). 80% FEV_1 predicted at 75 years is shown for comparison (orange).*

Modelling Older Subjects

- Figure 6 shows baseline results for a 63 year old healthy, male subject.
- Parameterisation of baseline model using peak muscle driving pressure, rate of decrease of airway diameter, maximum expiratory pressure (from PFTs) to measured values at age 63.
- Change in lung tissue compliance specified to be the same as that defined earlier at age 65 for younger subjects.
- % decrease in muscle pressure equivalent to that from previous study.
- No removal of terminal airways.
- Model prediction error results: FEV_1 12.5%, FEF_{25-75} 56.6%.
- Large discrepancy between calculated and actual PFTs. Airway closure not incorporated into model, therefore over-predicting results.

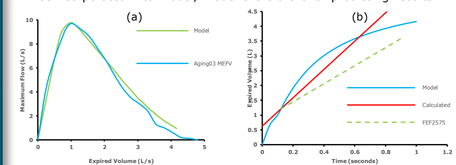

Figure 6. *Benchmark plots for healthy 63 year old. (a) shows volume flow plot for calculated solution (green) and PFT results (blue) for subject. (b) shows time volume plot from model (blue), calculated FEF_{25-75} (red) and actual FEF_{25-75} value from PFTs (green).*

- Figure 7 shows the extrapolated results for older subject at other decades.
- Results for changes in elastic recoil and muscle pressure only.
- Extrapolated FEV_1 at 25 years of age is 104% predicted for subject based on subject's height and age. (Subject's FEV_1 is 105% predicted at age 63)
- Figure 8 shows proportions of driving pressure for baseline solution indicating that the most sensitive subjects have smaller proportion of driving pressure contributed from muscle.

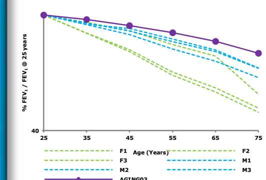

Figure 7. *Extrapolated results for older subject at decade intervals. Results overlaid on previous results for healthy young subjects (dashed lines).*

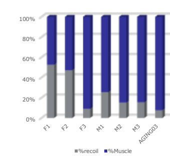

Figure 8. *Relative proportions of recoil and muscle pressure combining to generate required driving pressure for P_{ef} solution.*

Summary & Conclusions

- The model suggests that significant variation in decline of FEV_1 across subjects with age can be attributed to loss of elastic recoil interacting with the subject's specific airway geometry.
- Removing terminal bronchioles caused decline of FEV_1 and increased the age-dependent inter-subject variability, however without an accompanying decline in elastic recoil, very large numbers of terminal airways must be lost before FEV_1 decreases below the threshold of 80% predicted.
- Removal of terminal bronchioles had a more consistent effect across subjects (Figure 5) compared with loss of elastic recoil. Women were – on average – more sensitive to loss of recoil than men.
- Large decreases in tissue elasticity and numbers of terminal airways are possible before threshold for disease is reached (FEV_1 < 80% predicted).
- The results support the hypothesis that large numbers of terminal airways can be lost with age, without detection on forced spirometry.

Acknowledgements

This work was funded in part by MBIE grant 'Soft tissue mechanics for breast & lung'. DMV is a recipient of postdoctoral fellowships from the CIHR/IMPACT and the Canadian Thoracic Society. Volumetric imaging and pulmonary function data was supplied by the Division of Physiologic Imaging, Department of Radiology, University of Iowa (E.A.Hoffman).

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