THE QUANTITATIVE LINK OF LUNG CLEARANCE INDEX TO BRONCHIAL SEGMENTS AFFECTED BY BRONCHIECTASIS

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ONLINE SUPPLEMENT

Statistical Methods

Pearson and Spearman correlations, simple regression, analysis of covariance and stepwise linear multiple regression were conducted using Medcalc (v16.4.3, Mariakerke, Belgium) accepting statistical significance at P=0.05. Lung function indices were expressed in terms of %predicted and z-scores, based on normal data reported in Verbanck et al.[7] and according to the lambda-mu-sigma (LMS) method [ref OS1]. The gender, age and height dependent mu (M) for each lung function variable corresponds to the predicted value, while age and height dependent sigma (S) and constant lambda (L) serve to obtain z-score given by $[(x/M)^{L} – 1] / (L.S)$, where x is the measured value.

Limitations of the study

At the Brussels and Sydney sites, from where the prospective data (CF group) and retrospective data (nonCF group) derive, MBW setups were very similar as a result of a collaborative effort long before the study by Bilton et al.[6] Of note with respect to the data under study here, MBW and HCRT had been obtained on the same day at both sites. While being analyzed in the same way, the HRCT images in Sydney and in Brussels were acquired using different equipment and breathing protocols: at the end of a full inspiration in the nonCF patients from Bilton et al.[6] and during tidal breathing in our CF patients. All other things being equal, tidal breathing scans could lead to reduced airway size and hence lead to an underestimate of n_{BE}, but this would merely shift the

entire LCI vs n_{BE} plot to the left for the nonCF versus the CF patient group. Also, the images most likely to suffer from undetected bronchiectasis would be those from patients with a low number of n_{BE}, and we show that our correlations still hold when excluding these (e.g. Table 1: n_{BE}: 6-18). Another limitation concerns the fact that ventilation heterogeneity was roughly estimated here based on average CF patient characteristics (pre-inspiratory lung volume, tidal volume, anatomical dead space) whereas this computation could in principle be done on an individual patient basis. However, this degree of refinement in the quantification only really makes sense in a longitudinal setting with follow-up of both MBW and CT, or alternatively, in a cross sectional study where CT can be combined with MRI ventilation imaging and MBW testing. Here we merely set the stage for a potentially more detailed and personalized quantitative approach.

TABLE OS1 :

Correlation between number of segments affected by bronchiectasis (n_{BE}) and washout concentration MBW derived indices LCI and Curv.

Cystic Fibrosis patients (n=63; 24F)				correlation coeff (*)	P-value	95% CI for correlation coefficient
n_{BE}	LCI	n_{BE} : 0-18	(n=63)	0.72	<0.001	(0.57 - 0.82)
		n_{BE} : 6-18	(n=42)	0.52	<0.001	(0.25 - 0.71)
n_{BE}	Curv	n_{BE} : 0-18	(n=63)	0.69	<0.001	(0.53 - 0.80)
		n_{BE} : 6-18	(n=42)	0.50	<0.001	(0.24 - 0.70)
nonCF Bronchiectasis patients (n=15; 9F)						
n_{BE}	LCI	n_{BE} : 0-18	(n=15)	0.76	<0.001	(0.41 - 0.92)
n_{BE}	Curv	n_{BE} : 0-18	(n=15)	0.57	0.026	(0.08 - 0.84)

(*) Spearman rank correlation for non-normal distributed datasets.

n_{BE} : 6-18 corresponds to all patients with a bronchiectasis CT subscore greater than 1 (i.e., 2 or 3).

TABLE OS2 : CT subscores and resulting Bhalla score in main study group (CF) and ancillary data set (nonCF).

		Cystic Fibrosis patients (n=63)		nonCF Bronchiectasis patients (n=15)	
Category	(scoring range)	avg	SD	avg	SD
Severity of Bronchiectasis	(0-3)	1.7	1.0	1.7	0.7
Peribronchial Thickening	(0-3)	1.3	0.7	1.2	0.4
Extent of Bronchiectasis (nb of BP segments)	(0-3)	2.1	1.2	2.1	0.8
Extent of Mucus Plugging (nb of BP segments)	(0-3)	1.9	1.2	1.7	1.0
Sacculations or abcesses (nb of BP segments)	(0-3)	0.5	0.8	0.5	0.6
Generations of bronchial divisions involved	(0-3)	2.4	1.2	2.6	0.6
Nb of Bullae	(0-3)	0.2	0.7	0.0	0.0
Emphysema (nb of BP segments)	(0-2)	0.0	0.1	0.0	0.0
Collapse/Consolidation	(0-2)	0.4	0.6	0.7	0.8
BHALLA score	(25-0)	14.4	5.5	14.6	3.4

Figure OS1

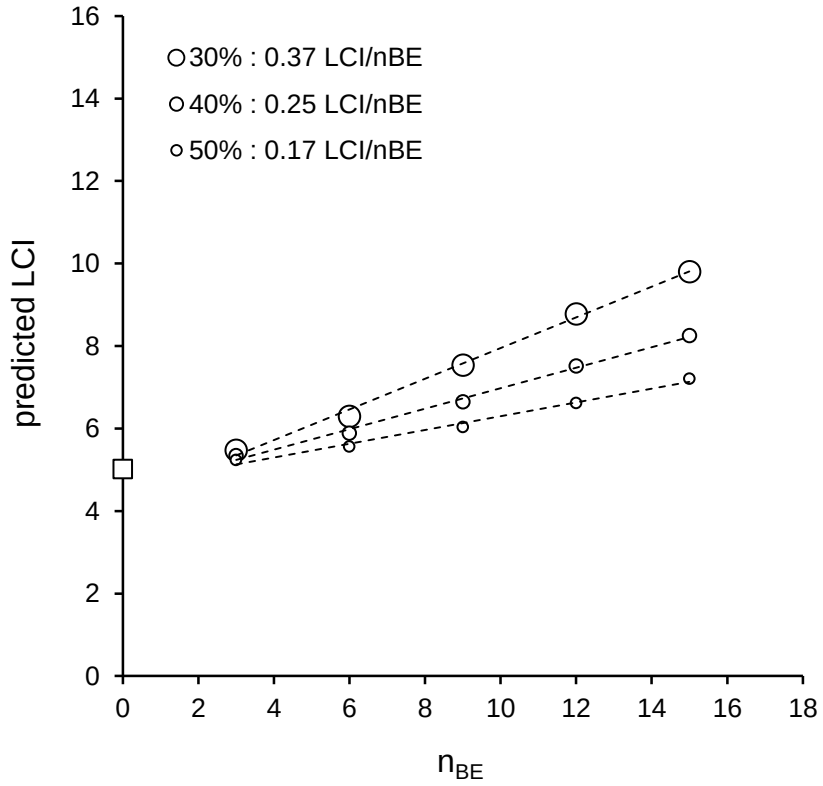
30% : 0.37 LCI/nBE
40% : 0.25 LCI/nBE
50% : 0.17 LCI/nBE
predicted LCI
0
2
4
6
8
10
12
14
16
18
n_{BE}

Figure OS2

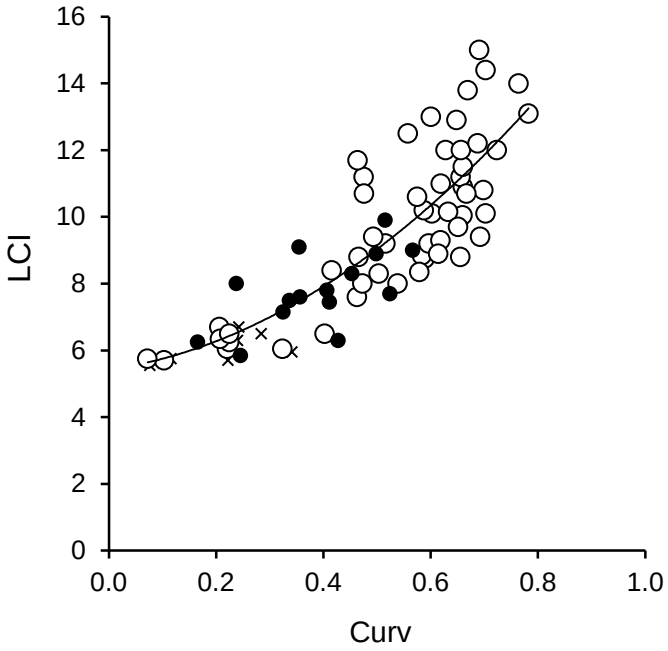

FIGURE LEGENDS

Figure OS1

Predicted increase of Lung Clearance Index (LCI) versus number of underventilated segments (50%,40% or 30% of normal ventilation) based on the compartment model described in ref[4,5], applied to 18 compartments, and using FRC=2.785L, tidal volume =1.130L, Fowler dead space 135ml, corresponding to the average values of the CF group. The open square represents the baseline value in case of normal ventilation. For the 3 cases of underventilation (open circles), a regression slope (ranging 0.2-0.4 LCI units per n_{BE}) is determined in the n_{BE} range 3-15, for comparison with the experimental regression slopes obtained in Figure 1A.

Figure OS2 :

Verification of the predicted curvilinear relationship between LCI vs Curv, as a hallmark of the convection-dependent ventilation heterogeneity described in [4]. Open circles: CF patients with at least one bronchopulmonary segment affected by bronchiectasis (n=54). Crosses: CF patients without bronchiectasis (n=9). Solid circles: nonCF patients with bronchiectasis (n=15).

REFERENCES

OS1. Cole TJ, Stanojevic S, Stocks J, Coates AL, Hankinson JL, Wade AM. Age- and size-related reference ranges: a case study of spirometry through childhood and adulthood. *Stat Med* 2009;28:880-98. Erratum in: *Stat Med* 2009;28(11):1644.