CORRESPONDENCE

Reasons for heterogeneous change in LCI in children with cystic fibrosis after antibiotic treatment

With great interest we read the paper of Horsley et al.[1] In their prospective observational study they showed significant improvement in indices of ventilation capacity (spirometry) and ventilation heterogeneity (multiple-breath washout (MBW)) after a course of intravenous antibiotics in subjects with cystic fibrosis (CF). There was considerable heterogeneity of lung clearance index (LCI) response as observed previously.[2] Here we aim to disentangle underlying physiological mechanisms of this heterogeneous response.

We assessed changes of lung function parameters before and after 23 courses of intravenous antibiotics in 19 children with CF aged 5–18 years. Children performed arterial blood oxygen measurement, nitrogen MBW,[3][4] body plethysmography and spirometry.

We observed a very heterogeneous change in LCI, with a mean decrease from 13.2 to 12.9, (p=0.41), and clear improvement in 7 of 23 subjects (>1 lung turnovers, see online supplementary figure S1). Spirometric indices improved significantly (see online supplementary table S1).

We found that change in LCI and moment ratio is best explained by change in functional residual capacity from MBW (FRC$_{MBW}$) minus residual volume (RV) (figure 1, see online supplementary figure S2). To our knowledge there is currently no established expression for this parameter.

In multivariable regression analysis, change of FRC$_{MBW}$—RV and ventilation homogeneity of conductive airways (Scond) explained 58% variability of delta LCI (R^2, see online supplementary table S2). These results suggest that improvement of LCI after antibiotic treatment in this patient group can be explained by: less secretion and obstruction (better ventilation of conductive airways=lower Scond), better ventilated lung units (net increase of expired tracer gas=FRC$_{MBW}$) and less hyperinflation (lower RV). Depending on the dominating effect and the resulting time constant of overall ventilated lung units,[2] LCI will change accordingly in the individual, explaining heterogeneous results.

The picture for moment ratio change is comparable, but understandably more influenced by peripheral ventilation
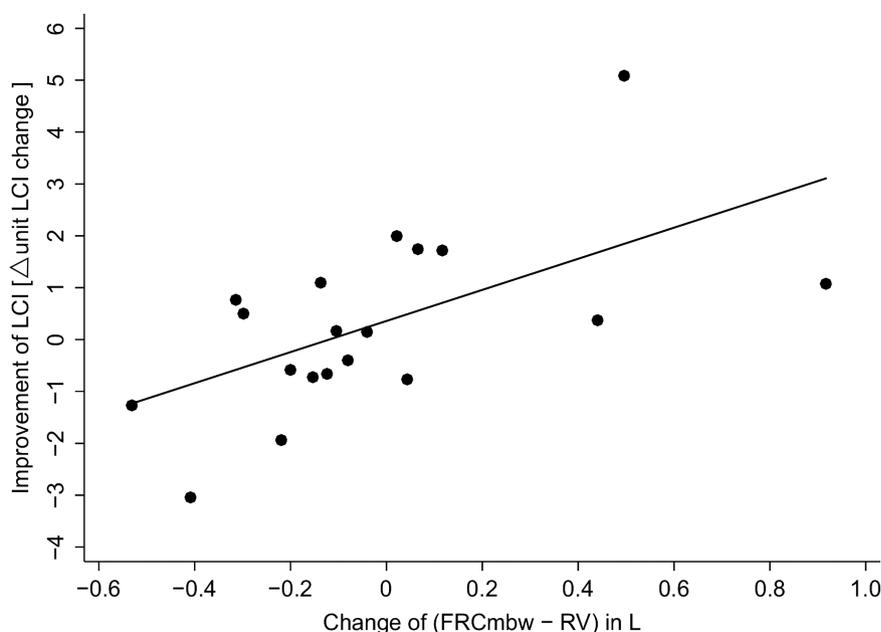

Figure 1 Association of lung clearance index (LCI) improvement and change in FRC$_{MBW}$—RV. Improvement of LCI (Δ LCI before minus after treatment) and change of functional residual capacity from nitrogen multiple-breath washout (FRC$_{MBW}$) minus residual volume (RV) from body plethysmography after 19 antibiotic courses in children with cystic fibrosis.

(Sacin) (see online supplementary table S3 and figure S2).

Change in abnormal LCI remains complex and is determined by several components contributing to overall ventilation heterogeneity, generated at different levels of the lung. We speculate that in severe CF lung disease airway collapse might hamper decrease of RV and consequently improvement of LCI. Thus, depending on the magnitude of reversibility of the single components, LCI seems to be a marker suited to monitor changes better[5] or less good in the course of CF lung disease.

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▶ http://dx.doi.org/10.1136/thoraxjnl-2013-204359

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Online supplement

Reasons for heterogeneous change in LCI in children with cystic fibrosis after antibiotic treatment

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Methods

We assessed changes (Δ) of lung function parameters before and after 23 intravenous (IV) antibiotic treatments in 19 children with cystic fibrosis (CF) aged 5-18 years. Thereof, two children had two and one child three IV courses, at least 5 months apart. Decision for IV antibiotics was made by the clinical CF team in 8 cases on routine basis, in 5 for *Pseudomonas aeruginosa* eradication and in 10 for a clinical pulmonary exacerbation.

Children performed arterial blood oxygen analysis from earlobe (paO_2), nitrogen multiple-breath washout (N_2 MBW) in a validated setup (1;2), body plethysmography and spirometry in this order. Primary outcome was lung clearance index (LCI) calculated as cumulative expired volume divided by functional residual capacity (CEV/FRC) with the unit lung turnover. Secondary outcomes were paO_2, moment ratio (MR), Scond and Sacin, forced expiratory flow in 1 second (FEV_1), forced vital capacity (FVC), forced expiratory flow between 25-75% expired maximal volume (FEF_{25-75}), the ratio of residual volume over total lung capacity (RV/TLC), RV and FRC from plethysmography (FRC_{pleth}). We then calculated (FRC_{pleth} minus FRC_{mbw}) as approximation for trapped gases and (FRC_{mbw} minus RV) as amount of expired tracer gas ($= FRC_{mbw}$) minus hyperinflated lung areas ($=$ RV). To our knowledge there is currently no established expression for this parameter.

Lung function parameters before and after IV antibiotics were compared using paired t-test. Abnormal lung function was defined as $\leq$ -2 z-scores. Linear regression analyses were performed to assess associations of different lung function parameters with Δ LCI or Δ MR. Parameters were entered separately into the model. We then used a backward stepwise exclusion strategy to obtain a final model of all parameters that were significantly associated with Δ LCI or Δ MR respectively (cut off p-value < 0.100). All analyses were done using Stata[TM] (Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

Median (range) age of the 19 children (7 boys) was 11.6 (4.8 − 17.8) years. In 9 of 23 antibiotic courses FEV_1 z-score before treatment was > -2, classifying for mild lung disease. Duration of the 23 IV antibiotic courses was of median (range) 14 (9 − 28) days. Lung function measurement was at median (range) plus one day (-6 to +3) of start and minus one day before end of treatment (-4 to +8). After treatment children showed a significant increase in weight.

LCI changed heterogeneously after IV antibiotics without reaching statistical significance, with a decrease from 13.2 to 12.9, a 2.0% change (p = 0.41), with clear improvement in 7 of 23 subjects (> 1 lung turnovers) (table 1). Statistical significant improvement was found for FEV_1 from 1.7 to 1.9 L, a 7.9% change (p = 0.026), and FVC from 2.3 to 2.4 L, a 5.9% change (p = 0.045). FEF_{25-75} improved from 1.4 to 1.6 L, a 16.2% change (p = 0.042). Statistical significance for FVC and FEF_{25-75} became weaker when comparing the latter transformed into z-scores. Neither RV/TLC nor RV, indicative for hyperinflation did change significantly. Detailed results of all measured parameters are listed in table 1.

In univariable regression analysis due to strong interrelation of several lung function parameters, many parameters were associated with Δ LCI (detailed results are given in table 2). In the final multivariable model Δ Scond and Δ FRC_{mbw} - RV were independently and strongly associated with Δ LCI (table 2). This model explained 58% (model R^2) of the LCI response. Results for Δ MR as outcome are given in table 3. In the final multivariable model Δ Sacin and Δ FRC_{mbw} − RV were independently associated with Δ MR, explaining 48% of the MR response.

We did not find differences in subgroups for age, gender, severity of disease (defined by FEV1 < -2 or > -2 z-score) or indication of antibiotic treatment. However subgroups tended to be rather small for more detailed analysis.

The 10 patients with LCI increase after treatment showed the following changes of the respective lung function parameters: 7/10 showed a decrease of FRC_{mbw}, 8/10 an increase of RV, 6/10 an increase of Scond and 9/10 an increase of trapped gas. Whether the reason for an increase in trapped gas and/ or increased hyperinflation in those patients is an airway collapse needs to be studied further.

Table 1. Summary of changes after antibiotic treatment.

	N	Before treatment	After treatment	Mean difference (95% CI)	p-value
Weight (kg)	23	37.1 (13.3)	38.0 (13.6)	0.9 (0.5 – 1.2)	<0.001
FEV_1 (L)	23	1.73 (0.64)	1.87 (0.76)	0.15 (0.02 – 0.27)	0.026
FEV_1 z-score	23	-2.21 (1.00)	-1.75 (1.32)	0.46 (0.09 – 0.83)	0.017
FVC z-score	23	-1.36 (1.15)	-0.99 (1.25)	0.38 (-0.02 – 0.77)	0.060
FEF_{25-75} z-score	23	-2.71 (0.94)	-2.35 (1.36)	0.36 (-0.03 – 0.74)	0.069
RV (L)	19	1.41 (0.69)	1.35 (0.60)	-0.06 (-0.19 – 0.07)	0.346
paO_2 (kPa)	15	69.3 (4.6)	72.3 (5.5)	3.0 (-1.0 – 7.0)	0.132
LCI	23	13.2 (2.5)	12.9 (2.8)	-0.3 (-1.0 – 0.41)	0.409
FRC_{mbw} (L)	23	1.83 (0.83)	1.78 (0.76)	-0.04 (-0.13 – 0.04)	0.301
CEV (L)	23	23.9 (11.8)	22.8 (11.0)	-1.2 (-2.5 – 0.15)	0.081
MR	23	19.5 (8.4)	18.7 (7.5)	-0.9 (-3.0 – 1.3)	0.406
Scond	23	0.084 (0.026)	0.079 (0.029)	-0.005 (-0.014 – 0.003)	0.207
Sacin	23	0.147 (0.067)	0.167 (0.079)	0.020 (-0.0004 – 0.041)	0.054
FRC_{mbw} – RV (L)	19	0.46 (0.41)	0.43 (0.49)	-0.03 (-0.19 – 0.14)	0.735
Trapped gas (L)	20	0.14 (0.34)	0.18 (0.34)	0.04 (-0.11 – 0.19)	0.592

Data before and after 23 courses of intravenous antibiotic treatment in 19 children with cystic fibrosis are given as mean (standard deviation). Data were compared by paired t-tests, mean difference is given with 95% confidence interval. Parameters from spirometry: Forced expiratory volume in

1 second (FEV$_1$), forced vital capacity (FVC) and forced expiratory flow between 25-75% expired maximal volume (FEV$_{25-75}$). From plethysmography: Residual volume (RV). Blood oxygen partial pressure (paO$_2$) was taken from arterialized earlobe. Parameters from triplicate nitrogen multiple-breath washout (MBW): Lung clearance index (LCI), functional residual capacity (FRC$_{mbw}$), cumulative expired volume (CEV), moment ratio (MR), Scond and Sacin. Combined parameters calculated from both measurements: FRC$_{mbw}$ - RV and FRC in plethysmography (FRC$_{pleth}$) minus FRC$_{mbw}$ as approximation for trapped gases.

Table 2. Associations of lung function parameters with improvement of lung clearance index after antibiotic treatment.

Δ LCI	Univariable model			Multivariable model		
	Coef.	95% CI	p-value	Coef.	95% CI	p-value
Baseline LCI (lung turnovers)	0.07	-0.22 – 0.35	0.632			
Δ Scond	-38.9	-70.0 – -7.8	0.017	-43.3	-70.8 – 15.7	0.004
Δ Sacin	-9.45	-24.12 – 5.23	0.195			
Baseline FEV1 (z-scores)	0.01	-0.71 – 0.74	0.966			
Δ FEV$_1$ (L)	2.36	0.12 – 4.59	0.039			
Δ FVC (L)	1.68	-0.38 – 3.75	0.105			
Δ FEF$_{25\text{-}75}$ (L)	0.79	-0.79 – 2.37	0.310			
Δ RV (L)	-2.32	-5.45 – 0.81	0.137			
Δ Trapped gas (L)	-3.00	-5.17 – -0.82	0.010			
Δ FRC$_{mbw}$ - RV (L)	3.10	1.03 – 5.17	0.006	3.14	1.49 – 4.79	0.001
Δ paO$_2$ (kPa)	0.11	-0.03 – 0.26	0.122			

Improvement of lung clearance index (Δ LCI) after antibiotic treatment, given per unit change (Δ = after − before treatment) of the respective variable: Baseline LCI, Δ Scond, Δ Sacin, z-score of baseline forced expiratory volume in 1 second (FEV1 z), Δ FEV$_1$, Δ forced vital capacity (FVC), Δ forced expiratory flow between 25-75% expired maximal volume (FEV$_{25\text{-}75}$), Δ residual volume (RV), Δ trapped gas estimated by the difference of FRC in plethsmography (FRC$_{pleth}$) minus FRC in multiple-breath washout (FRC$_{mbw}$), Δ FRC$_{mbw}$ minus RV and Δ arterial blood gas (paO$_2$). The final multivariable model shows the remaining exposure variables after backward exclusion of all variables with p > 0.1. The R^2 of the multivariable model was 58%, indicating how much of the variability of the improvement of LCI is explained by the parameters in the model.

Table 3. Associations of lung function parameters with improvement of moment ratio after antibiotic treatment.

Δ MR	Univariable model			Multivariable model		
	Coef.	95% CI	p-value	Coef.	95% CI	p-value
Baseline LCI (lung turnovers)	0.42	-0.32 – 1.17	0.248			
Δ Scond	-77.1	-181.5 – 27.4	0.140			
Δ Sacin	-40.5	-83.9 – 2.8	0.066	-39.3	-76-0 – -2.6	0.037
Baseline FEV1 (z-scores)	-1.07	-3.26 – 1.12	0.321			
Δ FEV_1 (L)	5.37	-1.86 – 12.61	0.138			
Δ FVC (L)	5.81	-0.44 – 12.06	0.067			
Δ FEF_{25-75} (L)	0.95	-4.04 – 5.93	0.697			
Δ RV (L)	-7.01	-16.42 – 2.40	0.134			
Δ Trapped gas (L)	-8.48	-15.21 – -1.68	0.017			
Δ FRC_{mbw} – RV (L)	9.53	3.38 – 15.68	0.005	9.42	3.88 – 14.96	0.002
Δ paO_2 (kPa)	0.36	-0.03 – 0.76	0.068			

Analogous to analysis in Table 2 but with improvement of moment ratio (Δ MR) as outcome after treatment. The final multivariable model shows the remaining parameters after backward exclusion of variables with p > 0.1. The R^2 of the multivariable model was 48%, indicating how much of the variability of the improvement of MR is explained by the parameters in the model.

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Figure legend

Figure 1. LCI before and after antibiotic treatment in children with CF. Mean lung clearance index (LCI) of triplicate nitrogen multiple breath washout before and after 23 courses of intravenous antibiotic treatment in 19 children with cystic fibrosis.

Figure 2. Association of MR improvement and change in FRC$_{MBW}$ - RV. Improvement of moment ratio (MR) (Δ MR before minus after treatment) and change of functional residual capacity from nitrogen multiple-breath washout (FRCmbw) minus residual volume (RV) from body plethysmography after 19 antibiotic courses in children with cystic fibrosis.
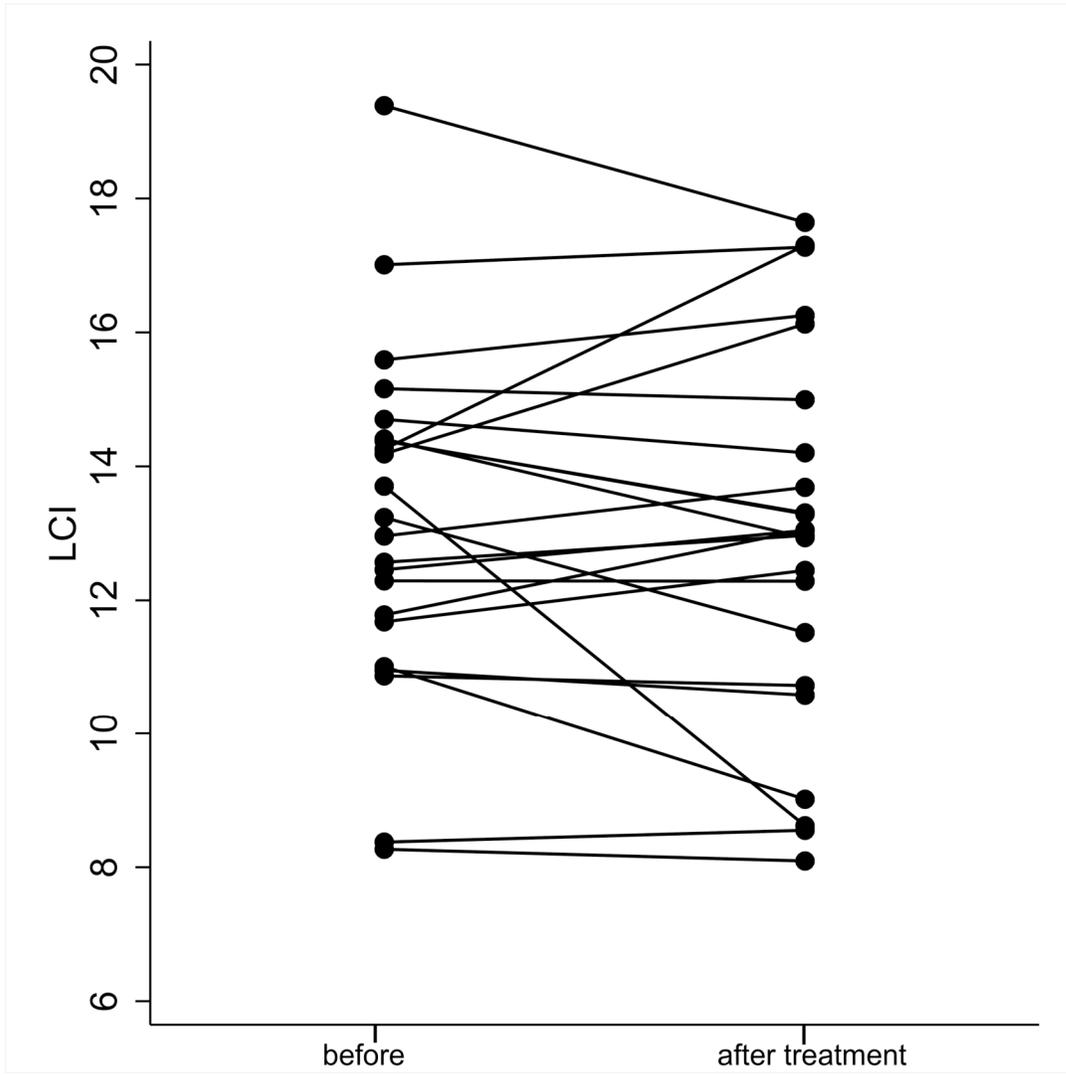
Figure 1.

Figure 2.