

## Author's response: heterogeneity of change in LCI in patients with cystic fibrosis following antibiotic treatment

I thank Yammine *et al* for their comments<sup>1</sup> on our paper.<sup>2</sup> In their interesting study, Yammine *et al*<sup>1</sup> have noted similar findings to those we described,<sup>2</sup> albeit in a less severely affected and younger population of cystic fibrosis (CF) patients. This raises important questions about what is happening in the lungs of CF patients during treatment for an exacerbation as well as the utility of lung clearance index (LCI) in this setting. It would appear that forced expiratory volume in 1 s (FEV<sub>1</sub>) is the more sensitive marker for change in this circumstance across a wide range of disease severities. Certainly the change in FEV<sub>1</sub> is more impressive than that in LCI, which is at least consistently inconsistent. Some patients show impressive improvements in LCI while others show major deteriorations, and the correlation with change in spirometry is at best modest.<sup>2</sup>

Yammine *et al*<sup>1</sup> have added plethysmography to this analysis, yet the results are somewhat disappointingly unenlightening. They did not observe any significant changes in measures of trapped gas with treatment. The major positive finding was that FRC<sub>MBW</sub>-RV was identified as a predictor of change in LCI in multiple regression analysis. This is a new composite measurement however, comprising variables obtained from different testing procedures, and the significance of this finding is unclear. The role of the phase III slope derived parameters S<sub>cond</sub> and S<sub>acin</sub> in this context is also unclear. As an analysis derived originally from the study of healthy adult lungs,<sup>3</sup> the underlying assumptions may not hold true in children with CF.<sup>4</sup> Finally, the use of nitrogen as a tracer gas may complicate comparison with studies using sulphur hexafluoride, and indeed improvements in heterogeneity might even lead to worsening of LCI.<sup>5</sup>

This does not detract from the use of LCI in stable patients, where it has proven to be a useful and sensitive marker. The situation in exacerbations is complicated by significant heterogeneity in the severity of exacerbation and subsequent physiological impact, as well as the range of additional therapies and interventions that patients undergo. Although we may differ

on the finer points of methodology, the conclusion that LCI is both complex and affected by several different competing components is entirely in accord with our own observations. As the authors note, it is likely however that the relative importance of different processes differ between patients, but so far we have not perfected the tools to accurately identify these from the washout curves. Ongoing imaging studies using hyperpolarised He<sup>3</sup> MRI alongside LCI offer the greatest chance of shining a light on the complex evolution and resolution of ventilation heterogeneity.<sup>6</sup> These will hopefully afford a functional standard against which to compare both new and old measures of gas mixing physiology that can then be applied in clinical practice.

### Alex Horsley<sup>1,2</sup>

<sup>1</sup>Institute of Inflammation and Repair, University of Manchester, Manchester, UK

<sup>2</sup>Manchester Adult Cystic Fibrosis Centre, University Hospital of South Manchester, Manchester, UK

**Correspondence to** Dr Alex Horsley, Manchester Adult Cystic Fibrosis Centre, University Hospital of South Manchester, Manchester, M239LT, UK; alexander.horsley@manchester.ac.uk

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