Supine posture changes lung volumes and increases ventilation heterogeneity in cystic fibrosis

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Abstract

Introduction

Lung Clearance Index (LCI) is recognised as an early marker of cystic fibrosis (CF) lung disease. The effect of posture on LCI however is important when considering longitudinal measurements from infancy and when comparing LCI to imaging studies.

Methods

35 children with CF and 28 healthy controls (HC) were assessed. Multiple breath washout (MBW) was performed both sitting and supine in triplicate and analysed for LCI, S_{cond}, S_{acin}, and lung volumes. These values were also corrected for the Fowler dead-space to create 'alveolar' indices.

Results

From sitting to supine there was a significant increase in LCI and a significant decrease in FRC for both CF and HC ($p<0.01$). LCI, when adjusted to estimate 'alveolar' LCI (LCI_{alv}), increased the magnitude of change with posture for both LCI_{alv} and FRC_{alv} in both groups, with a greater effect of change in lung volume in HC compared with children with CF. The % change in LCI_{alv} for all subjects correlated significantly with lung volume % changes, most notably tidal volume/functional residual capacity (Vt_{alv}/FRC_{alv} ($r = 0.54, p<0.001$)).

Conclusion

There is a significant increase in LCI from sitting to supine, which we believe to be in part due to changes in lung volume and also increasing ventilation heterogeneity related to posture. This may have implications in longitudinal measurements from infancy to older childhood and for studies comparing supine imaging methods to LCI.

Introduction

Multiple breath washout (MBW) is recognised as an important clinical and research method in cystic fibrosis (CF) [1]. Indices derived from MBW reflect the degree of ventilation heterogeneity within the lungs. The lung clearance index (LCI) is thought to reflect overall ventilation heterogeneity, whereas the phase III slope indices S_{cond} and S_{acin} are proposed indices of heterogeneity in the washout signal from the convection and diffusion-convection dependent airways respectively [2]. LCI in particular has been extensively investigated and is an important measure of early lung disease in CF [3, 4] and is well suited to a paediatric age group with relatively mild lung disease.

The effect of posture on LCI in children with CF has recently been assessed [5]. This study compared CF children with mild disease to healthy controls (HC) and showed that LCI in the supine posture was elevated when compared to sitting and that supine LCI correlated better than sitting LCI with metrics derived from high resolution computed tomography (HRCT). The authors also reported that the magnitude of the increase in LCI was greater in CF children than HC, despite similar reductions in FRC. This postural effect is also important when assessing longitudinal changes in LCI, with infant MBW performed supine whilst older children tend to perform the measurements sitting. The effect of this change in posture is therefore important for the interpretation of changes in LCI.

One major effect of the supine posture is the impact that this has on lung volumes. In particular, a reduction in FRC when lying supine compared to an upright posture is widely reported [6].

LCI is calculated using the FRC and several authors have shown that LCI can be affected by large changes in lung volumes [7–9]. Understanding the effect of posture on ventilation heterogeneity may allow more accurate comparisons with imaging and relate structural abnormalities to lung physiology and will aid in the interpretation of longitudinal studies in young children.

Further to the work of Ramsey et al [5], the aim of this study therefore was to compare LCI and the phase III slope parameters S_{cond} and S_{acin}, sitting and supine, in children with a range of CF lung disease as well as in HC, and to measure the extent to which changing lung volume affects the change in LCI. We hypothesised that supine posture would firstly reduce lung volume (FRC) with a resultant effect on gas mixing, but also that there would be an additional effect of posture on ventilation heterogeneity within the lungs.

Methods

This was an observational study performed at two specialist UK paediatric centres: Sheffield Children's Hospital (SCH) and Royal Hospital for Sick Children, Edinburgh (RHSC). This study was approved by the National Research and Ethics Committee (SCH—REC 12/YH/0343. RHSC—Lothian Research Ethics Committee (08/S1101/290)) and parents/guardians provided written informed consent.

Subjects with CF had a clinical diagnosis confirmed via sweat testing and/or genetic testing and were clinically stable, without exacerbation for at least 4 weeks prior to assessment. HC were without chronic respiratory illness, neuromuscular weakness or bone disease likely to impair respiration and with no congenital cardiac disease requiring medication. HC also had no history of acute respiratory illness in the 4 weeks prior to testing. Children were aged 5–16 years old.

LCI values from SCH CF (n = 19) and HC (n = 10) children have previously been reported [10]. This previous work reported the sensitivity of LCI to detect lung disease in comparison to helium-3 MRI, spirometry and CT. This report did not compare the sitting LCI to that

performed in the supine posture. The current study also contains additional analyses to explore the causes of the changes in LCI on lying supine.

All subjects performed MBW using a modified open-circuit Innocor device with (0.2%) sulfa-hexaflouride (SF_6) as the tracer gas for wash-in and room air for washout [11]. MBW was measured in triplicate without randomisation with regards the order of sitting and supine measurements. MBW was firstly performed seated and then supine, followed by spirometry. Spirometry was performed according to international guidelines [12] using a 'PFT Pro' (Carefusion, Basingstoke, UK) in the SCH cohort and using an 'Easyone' (ndd, Zurich, Switzerland) in the RHSC cohort. The SCH cohort did not pause after the supine posture was adopted before performing MBW, whilst the RHSC cohort waited 30 minutes whilst supine before starting MBW.

The Innocor MBW system was used in both centres as previously described [11]. Each subject breathed tidally through a low dead-space filter and flanged mouthpiece (adapted to ensure minimal dead-space) attached in series to a pneumotachograph (Hans-Rudolph, USA). During the wash-in, an open bias flow circuit was attached to the distal end of the pneumotachograph, supplying 0.2% SF_6 in air at a flow rate of 10-12lpm from a gas cylinder. Each subject was encouraged to breathe naturally whilst being distracted by watching a DVD until the difference between the inspired and expired concentration of SF_6 was <0.004%. The subject was then disconnected from the flow-past circuit during exhalation, after which the subject continued tidal breathing until the expired concentration of SF_6 dropped below 1/40th of the initial concentration (approximately 0.005%) for three consecutive breaths.

MBW data were analysed using custom-built software for the measurements of LCI, S_{cond} and S_{acin}, FRC, tidal volume ((Vt) taken as the average across all washout breaths) and Fowler dead-space (FDS) [13], with the final result being the average value recorded from at least 2 acceptable trials [14]. LCI was calculated as the cumulative expired volume required to 'washout' the tracer gas to 1/40th of the 'washed-in' concentration, divided by the FRC. Phase III slope analysis was automated and checked manually to confirm accurate identification of alveolar slopes. S_{acin} was calculated from the first expiratory breath after the wash-in was complete. S_{cond} was calculated from breaths during 1.5–6 lung turnovers as previously described [14]. Spirometric measures of FEV_1, FVC and FEV_1/FVC were expressed as z-scores using recommended equations [15].

Methods for alveolar indices of MBW

Alveolar indices were calculated as previously described [16]. FDS [17] was calculated from the exhaled CO_2 curve measured at each breath of the wash-out and the average from all breaths recorded. Alveolar lung volumes were then calculated by subtracting the FDS from the lung volumes to create FRC_{alv} and Vt_{alv}. LCI_{alv} was calculated using the formula:

$$LCI_{alv} = \frac{(CEV - (FDS \times B))}{(FRC - FDS)}$$

Where CEV is the cumulative expired volume required to wash-out SF_6 to 1/40th of the starting concentration and B is the number of tidal breaths required to do the same.

Statistical analysis

Comparisons between CF and HC were performed using un-paired t-tests or Mann-Whitney tests after assessing for the normal distribution. Comparisons between sitting and supine measurements made in the same subjects were performed using paired t-tests or the Wilcoxon matched-pairs signed rank test. Correlations were performed using either Pearson or Spearman

rank analysis. A p-value of <0.05 was considered statistically significant and presented throughout the manuscript alongside the mean or median difference (MD) and the 95% confidence intervals (CI) where appropriate. All analysis was performed using GraphPad Prism V7 (San Diego, USA). Height and weight were converted into age-appropriate z-scores [18].

Results

35 children with CF (19 from SCH) and 28 HC (10 from SCH) completed both the sitting and supine MBW assessments. Demographic and baseline lung function data are summarised in Table 1. HC subjects were significantly taller and heavier than CF subjects (MD (95% CI): height z-score = -0.73 (-1.24, -0.22,), p = 0.006. Weight z-score = -0.43 (-0.79, 0.00), p = 0.049)) and non-significant trends of greater age in HC. CF subjects had significantly poorer lung function outcomes than HC, with lower FEV_1 and FEV_1/FVC z scores as well as increased sitting LCI and S_{cond}. Despite this, in CF subjects the overall mean z-scores for FEV_1 and FEV_1/FVC were -0.78 and -0.89 respectively, and therefore within the normal reference range (z-score >-1.64). 8/35 CF subjects had an FEV_1 z-score <-1.64, and 6/35 had an FEV_1/FVC z-score <-1.64. In contrast, 17/35 subjects had an LCI (sitting) greater than the upper limit of normal (7.4) [11]. All HCs had normal FEV_1, FEV_1/FVC and LCI (sitting).

Combined CF and HC demographics compared between each testing centre were not significantly different. CF patients from SCH were however, slightly older than RHSC (mean age = 10.93 vs 9.06 years, p = 0.049) and therefore also taller (mean height = 142.8 vs 130.8cm, p = 0.039). There were no significant differences when comparing the % change in LCI, FRC, CEV, Vt or Vt/FRC between subjects measured from the two different centres. The SCH cohort demonstrated no significant difference or consistent effect between supine MBW trial 1 and trial 3 (p = 0.68).

Changes with posture

There were large and statistically significant reductions in FRC when changing from the sitting to supine posture, in both CF and HC, of 24.40% (95% CI = 20.95, 27.85) and 28.42% (95%

Table 1. Demographics and baseline lung function data for healthy control and cystic fibrosis subjects.

	Healthy Controls	Cystic Fibrosis	Mean or median difference (95% CI)	p value
Number of subjects	28	35		
Sex (M/F)	16/12	16/19		
Age (years)	11.53 (3.39)	10.07 (2.82)	-1.45 (-3.02, 0.11)	0.068
Height (cm)	150.30 (20.27)	137.30 (17.30)	-12.99 (-22.46, -3.52)	0.008
Height z-score	0.59 (0.96)	-0.14 (1.04)	-0.73 (-1.24, -0.22,)	0.006
Weight (kg)	44.54 (18.46)	35.49 (13.68)	-7.15 (-17.3, 0.3)	0.065
Weight z-score	0.57 (0.97)	0.23 (0.76)	-0.43 (-0.79, 0.00)	0.049
FEV_1 (z-score)	-0.07 (0.86)	-0.78 (1.31)	-0.52 (-1.09, -0.04)	0.033
FEV_1/FVC (z-score)	-0.09 (0.81)	-0.89 (0.80)	-0.78 (-1.21, -0.33)	<0.001
LCI (sitting)	6.25 (0.41)	7.72 (1.68)	1.04 (0.60, 1.64)	<0.001
LCI (supine)	6.47 (0.40)	8.22 (1.86)	1.1 (0.66, 1.76)	<0.001
FRC (L) (sitting)	1.85 (0.78)	1.25 (0.43)	-0.44 (-0.77, -0.19)	<0.001
S_{cond} (sitting)	0.02 (0.01)	0.05 (0.02)	0.03 (0.02, 0.05)	<0.001
S_{acin} (sitting)	0.10 (0.04)	0.15 (0.09)	0.02 (-0.01, 0.05)	0.087

Values are expressed as mean (SD). Mann-Whitney tests demonstrate whether the two groups significantly differ for each outcome, with the exception of age and height, which were assessed using un-paired t-tests. The mean or median difference, 95% confidence intervals and p-value are presented.

CI = 23.92, 32.91) respectively (both p<0.001) (see Table 2, Fig 1). There were small but statistically significant increases in LCI. In HC, mean LCI increased by 3.63% from 6.25 to 6.47 (MD (95% CI) = 0.17 (0.06, 0.36), p<0.001) and in CF LCI increased by 6.69% from 7.72 to 8.22 (MD (95% CI) = 0.34 (0.17, 0.72), p<0.001). There were also large and statistically significant reductions in CEV. In CF, mean CEV decreased by 20.00% (95% CI = 16.00, 24.90) and in HC by 25.40% (95% CI = 21.22, 29.63). Adjusting FRC for height by expressing as a percentage of predicted did not change the pattern of results.

Bland-Altman analysis of sitting and supine LCI (Fig 2) demonstrates that the effect of posture on LCI is greater in CF subjects than HC. CF subjects had an increased mean difference (CF = 0.5, HC = 0.22) and wider 95% limits of agreement (2.11, -1.11) when compared to HC (0.83, -0.39).

In CF, supine posture was associated with significant decreases in both Vt (Mean (95% CI) = -8.0% (-12.7, -3.4)) and FDS (Mean (95% CI) = -8.4% (-12.5, -4.3)), whereas in HC neither of these variables showed significant change. In both CF and HC however, the large reductions in FRC led to significant increases in the ratio of Vt/FRC (Mean (95% CI) = 24.0% (14.92, 33.07) and 54.5% (37.2, 71.9) increase respectively).

S_{cond} was low in HC and increased from 0.02 sitting, to 0.03 supine (MD (95% CI) = 0.01 (-0.01, 0.02), p = 0.028). There were no statistically significant changes in other phase III slope indices.

Analysis of alveolar MBW

Correcting MBW for FDS to produce measures of ventilation heterogeneity independent of changes in physiological dead space did not alter the pattern of changes described above when moving from a sitting to a supine posture. Correcting for FDS increased the magnitude of the postural effect on LCI in both groups (Mean (95% CI) increase of 9.6% (5.5, 13.6) in CF and

Table 2. Sitting to supine comparison of multiple breath washout (MBW) outcomes for both cystic fibrosis (CF) and healthy control (HC) subjects.

	Sitting	Supine	% Change	Mean or median difference (95% CI)	p value
LCI HC	6.25 (0.4)	6.47 (0.4)	3.63 (5.26)	0.17 (0.06, 0.36)	<0.001
LCI CF	7.72 (1.68)	8.22 (1.86)	6.69 (10.41)	0.34 (0.17, 0.72)	<0.001
FRC HC (L)	1.85 (0.78)	1.32 (0.64)	-28.42 (11.59)	-0.47 (-0.66, -0.34)	<0.001
FRC CF (L)	1.25 (0.43)	0.93 (0.30)	-24.40 (10.04)	-0.28 (-0.34, -0.21)	<0.001
Vt HC (L)	0.45 (0.20)	0.46 (0.20)	7.72 (28.01)	0.01 (-0.04, 0.06)	0.682
Vt CF (L)	0.42 (0.15)	0.39 (0.15)	-8.04 (13.46)	-0.03 (-0.07, -0.01)	<0.001
Vt/FRC HC (%)	25.61 (10.50)	37.5 (14.40)	54.5 (44.78)	11.68 (6.75, 15.53)	<0.001
Vt/FRC CF (%)	35.62 (12.92)	42.96 (14.47)	24.00 (26.42)	7.46 (3.86, 10.96)	<0.001
CEV HC (L)	11.54 (4.7)	8.63 (4.04)	-25.43 (10.84)	-2.73 (-3.74, -2.01,)	<0.001
CEV CF (L)	9.79 (4.09)	7.77 (3.41)	-20.43 (12.97)	-1.79 (-2.53, -1.17)	<0.001
FDS HC (L)	0.09 (0.03)	0.09 (0.03)	8.20 (52.37)	-0.01 (-0.01, 0.01)	0.597
FDS CF (L)	0.08 (0.02)	0.08 (0.02)	-8.39 (11.82)	-0.01 (-0.01, 0.00)	<0.001
S_{cond} HC	0.02 (0.01)	0.03 (0.01)	101.80 (135.90)	0.01 (-0.01, 0.02)	0.028
S_{cond} CF	0.05 (0.02)	0.06 (0.03)	29.60 (59.71)	0.01 (-0.01, 0.16)	0.051
S_{acin} HC	0.10 (0.04)	0.09 (0.04)	-11.71 (41.58)	-0.01 (-0.03, 0.01)	0.117
S_{acin} CF	0.15 (0.09)	0.14 (0.10)	6.50 (42.48)	0.01 (-0.02, 0.02)	0.721

Values are expressed as mean (SD). Wilcoxon tests were calculated to assess whether the sitting to supine change was significantly different, with the exception of FDS HC, S_{cond} CF and S_{acin} HC, which were calculated using paired t-tests. The mean or median difference, 95% confidence intervals and p-value are presented.

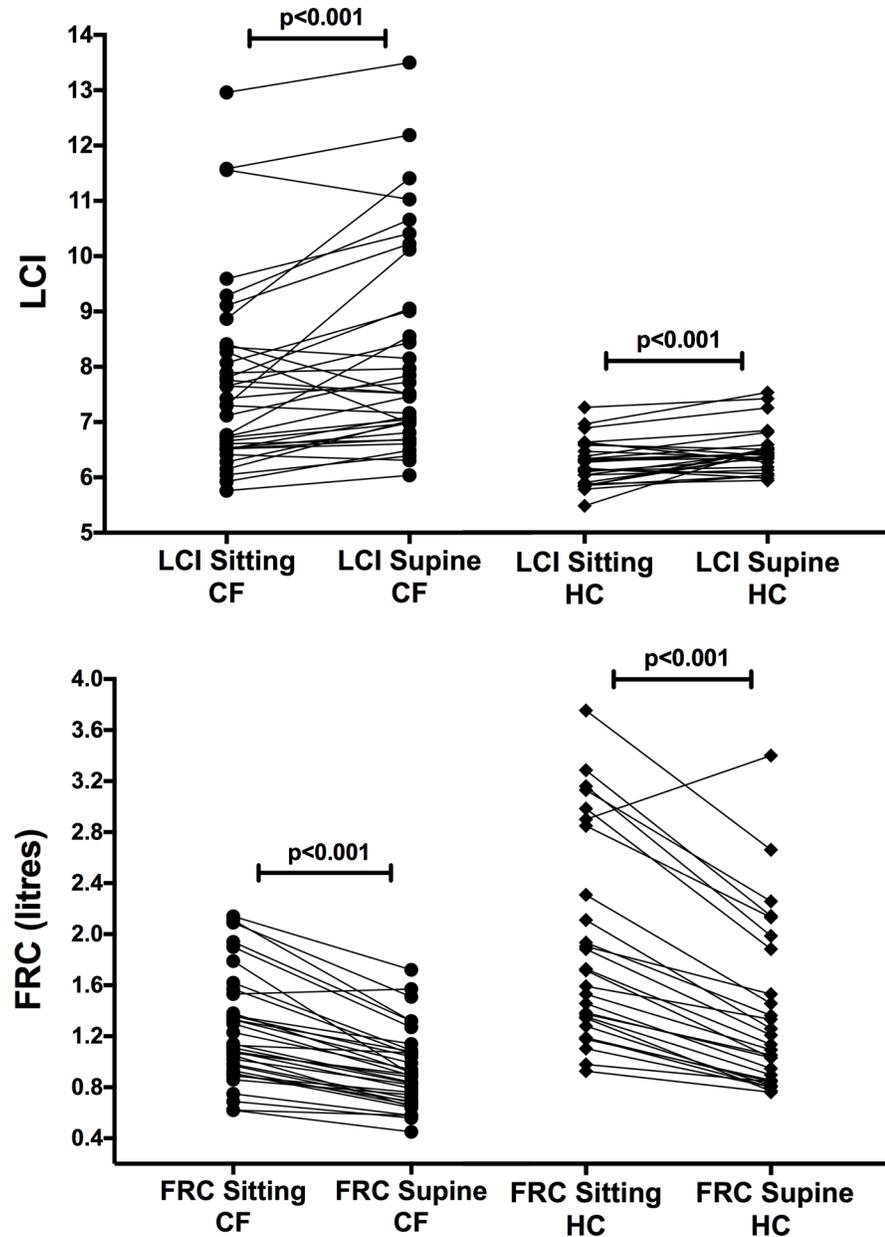https://doi.org/10.1371/journal.pone.0188275.t002

Fig 1. LCI and FRC change from sitting to supine in both cystic fibrosis (CF) and healthy controls (HC). There is a significant increase in LCI from sitting to supine in both CF and HC and a significant decrease in FRC.

8.6% (5.7, 11.6) increase in HC) and the decrease in FRC (Mean (95% CI) = -25.4% (-29.2, -21.7) in CF and -29.4% (-34.2, -24.6) in HC) (Table 3). HC subjects had a significantly larger % change in Vt_{alv}/FRC_{alv} than CF but there was no group difference for the % change in LCI_{alv} (Table 4).

Correlations

In the combined CF and HC data, the difference in LCI from sitting to supine and the % change in LCI, resulted in no significant correlations with any baseline or % change value. For
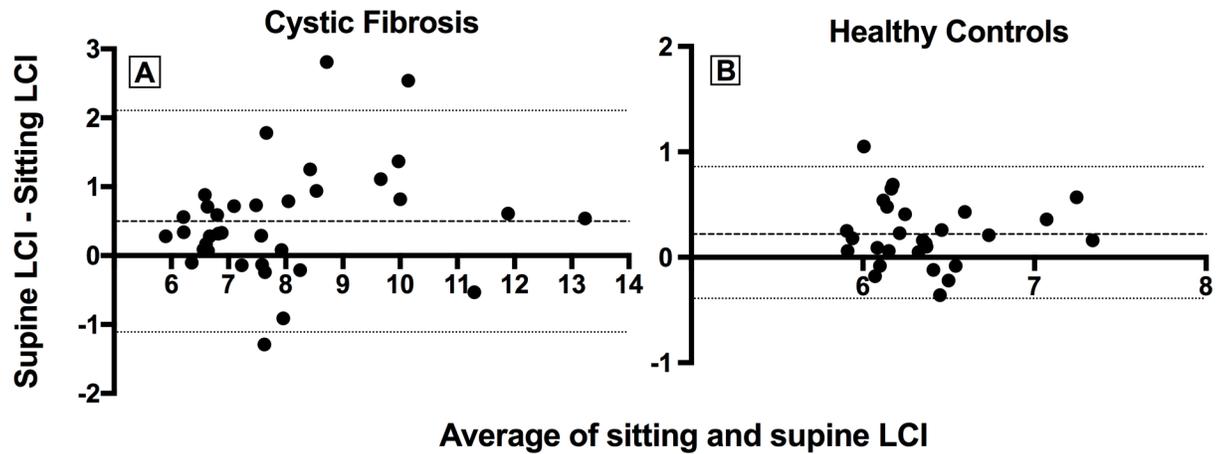
Fig 2. Bland-Altman analysis of sitting and supine LCI in children with CF (A) and healthy controls (B). The dashed line indicates the mean difference and the dotted lines indicate the 95% limits of agreement.

the combined CF and HC populations, the % change in LCI_{alv} however showed significant correlations with the % change in FRC_{alv} (r = -0.47, p<0.001), % change in Vt_{alv} (r = 0.38, p = 0.002) and the % change in Vt_{alv}/FRC_{alv} (r = 0.54, p<0.001, Fig 3). Individually, the % change in Vt_{alv}/FRC_{alv} against % change in LCI_{alv} was better correlated in HC (r = 0.71, p<0.001) than in CF (r = 0.50, p = 0.002).

Discussion

These results demonstrate that subjects with CF and predominantly mild lung disease increase LCI when changing posture from sitting to supine, with an associated significant reduction in FRC. This study adds to previously reported data by interrogating possible causes for the increase seen in LCI including the effects of dead-space and the change in different lung volumes due to posture [5]. When assessing lung volumes measured during MBW, in addition to a reduction in FRC, we also demonstrate in CF subjects that adopting the supine posture resulted in a decrease in Vt and FDS. All subjects had a significant increase in the ratio of Vt/FRC and decrease in CEV.

Table 3. Sitting to supine comparison of 'alveolar' multiple breath washout outcomes.

	Sitting	Supine	Mean or median difference (95% CI)	p-value
LCI_{alv} HC	5.16 (0.29)	5.60 (0.43)	0.44 (0.29, 0.59)	<0.001
LCI_{alv} CF	6.65 (1.47)	7.27 (1.66)	0.59 (0.3, 10.73)	<0.001
FRC_{alv} HC (L)	1.77 (0.77)	1.25 (0.63)	-0.44 (-0.69, -0.33)	<0.001
FRC_{alv} CF (L)	1.17 (0.41)	0.86 (0.29)	-0.27 (-0.34, -0.2)	<0.001
Vt_{alv} HC (L)	0.37 (0.17)	0.38 (0.20)	-0.01 (-0.04, 0.05)	>0.99
Vt_{alv} CF (L)	0.34 (0.15)	0.31 (0.14)	-0.03 (-0.05, 0.00)	0.005
Vt_{alv}/FRC_{alv} HC (%)	22.64 (10.02)	32.94 (15.34)	7.79 (5.32, 12.04)	<0.001
Vt_{alv}/FRC_{alv} CF (%)	30.83 (13.36)	37.78 (15.18)	6.62 (3.36, 9.94)	0.001

Alveolar outcomes were calculated using the method of Haidopoulou et al (2012) [16] which corrects outcomes for the fowler dead-space. Values are expressed as mean (SD). Wilcoxon tests were calculated to determine whether the sitting to supine change was significantly different, with the exception of LCI_{alv} HC, which was calculated using paired t-tests. The mean or median difference, 95% confidence intervals and p-value are presented.

Table 4. A comparison of the % change in 'alveolar' multiple breath washout outcomes between healthy controls and cystic fibrosis subjects.

% Change	Healthy controls	Cystic fibrosis	Mean or median difference (95% CI)	p-value
LCI_{alv}	8.62 (7.45)	9.57 (11.74)	0.38 (-3.76, 5.31	0.844
FRC_{alv}	-29.43 (12.15)	-25.43 (10.88)	5.00 (0.19, 9.47)	0.042
Vt_{alv}	3.75 (24.53)	-7.95 (15.19)	11.7 (1.56, 21.83)	0.024
Vt_{alv}/FRC_{alv}	50.63 (44.15)	27.16 (30.69)	23.47 (4.45, 42.49)	0.017

Comparsions made using un-paired t-tests, with the exception of LCI_{alv} and FRC_{alv}, which were calculated using Mann-Whitney tests. The mean or median difference, 95% confidence intervals and p-value are presented.

The increase in LCI with change in position suggests this change of posture increases ventilation heterogeneity in both CF and HC. The relative (%) change however did not correlate with other measured baseline parameters, including other markers of disease severity. There were inconsistent changes in S_{cond} and S_{acin} when adopting the supine posture, we are therefore unable to determine whether the increasing heterogeneity was specifically related to changes in conductive or acinar airway heterogeneity.

Alveolar LCI

To assess whether increased LCI was due to increasing ventilation heterogeneity and not due to changes in physiological dead-space, the method of Haidopoulou [16] was used to calculate the 'alveolar' LCI (LCI_{alv}). This involves subtracting the Fowler dead-space from the lung volume components and reduces LCI. The observation that LCI_{alv} has a greater increase than LCI from sitting to supine confirms that increased supine LCI is not simply a mathematical
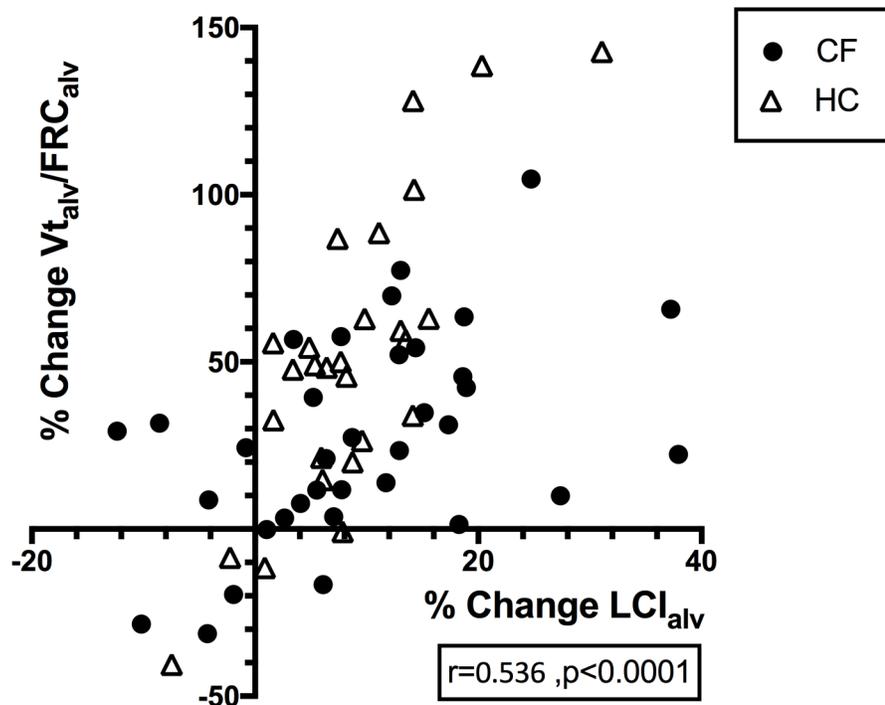

Fig 3. Scatter plot with Spearman correlation of the % change in the 'alveolar' Vt_{alv}/FRC_{alv} with the % change in 'alveolar' LCI_{alv} for both cystic fibrosis (CF) and healthy control (HC) subjects combined. The Spearman correlation suggests a positive relationship between increasing % change Vt_{alv}/FRC_{alv} and increasing % change LCI_{alv}.

consequence of reducing FRC. Correcting for the dead-space also changed the relationship between the outcomes, such that the % change in LCI_{alv} became significantly correlated with the mean Vt_{alv}, FRC_{alv} and therefore the Vt_{alv}/FRC_{alv} ratio. The correlation between the % change in Vt_{alv}/FRC_{alv} and LCI_{alv} was stronger in HC than CF suggesting that the change in lung volumes, from sitting to supine, is a more important factor in the change in LCI in subjects without airways disease. In patients with CF, even in those with mild disease, there is a less predictable effect of posture on the distribution of ventilation.

Consistent with this, CF subjects also had a poorer agreement between LCI values measured sitting and supine than HC, again suggesting that CF lungs have a more unpredictable gas mixing response to the supine posture than HC.

Relevance

Imaging studies performed supine, such as MRI [10, 19–21] and CT [22] are increasingly used to assess the earliest changes in the CF lung. MBW performed while seated is also being used to provide regional insight to the structural and physiological changes measured in MBW [23]. In addition, longitudinal studies in young children with CF often compare measurements performed in infancy while supine, with repeated measurements performed seated in later childhood. Age related change in posture when measuring LCI should also be taken into consideration when interpreting longitudinal studies. The results of this study suggest; (i) that the supine posture changes LCI, (ii) that the amount it changes by is not predictable in an individual and (iii) that there is likely a true increase in ventilation heterogeneity [5]. Due to the inherent nature of how LCI is calculated, a change in FRC and Vt/FRC will lead to a change in LCI [9]. Our results suggest that the increase in LCI seen in CF is related to changes in ventilation heterogeneity. Therefore, subject posture should be taken into consideration when making direct physiological comparisons between MBW and imaging outcomes[5] and when assessing longitudinal measurements.

Our findings are predominantly aligned with those previously reported, except we found no significant difference in the amount of change in LCI, from sitting to supine, between CF and HC [5]. The reason for this difference is not clear, though it may relate to the different MBW gases used;. SF_6 wash-in and washout as reported here and a Nitrogen (N_2) washout methodology previously reported[5]. LCI derived from SF_6 measurement is likely to differ from N_2 LCI methodology[14], due to the differing gas properties and also possible affects of N_2 resident in the lung and excreted from alveolar tissue. There are also discrepancies with regards FRC measurements from differing N_2 washout systems, [24, 25] which may also have an impact on postural measurements. The CF cohort reported has a younger mean age (by approximately 2 years), with a lower mean sitting LCI than previously reported [5], however the HC cohorts have a similar disparity in sitting LCI in both studies. This makes it difficult to determine whether there is therefore a true difference in disease severity of the two CF cohorts or whether the difference is due to differing MBW methodologies.

Imaging studies demonstrate that ventilation gradients are present in healthy lungs, that are liable to change when lying supine [26] or in microgravity [27]. Supine changes in LCI may therefore be due to altered gravitational forces. Such changes appear poorly predictable in CF lungs where there is greater variation in regional lung compliance and airway calibre than the healthy lung [28]. This may also explain why children with asthma [29] and adults with chronic heart failure [30] demonstrate no change in LCI when lying supine despite similarly reduced FRC. In this study we have only assessed patients with predominantly mild CF, but it is possible that the effect may be more profound or more unpredictable in those with more severe disease.

Mucus plugging and bronchiectasis are common features in CF lungs [28]. It is possible that when lying supine, where the distribution of ventilation causes increased inter-regional ventilation heterogeneity [31], that any peripheral areas of bronchiectasis and mucus plugging receive a greater distribution of ventilation compared to an upright posture, causing an increase in ventilation heterogeneity and therefore LCI.

Study limitations

Data collection for this study was carried out at two separate centres, with the data combined. Subjects from RHSC waited for 30 minutes in the supine posture before measuring MBW whilst SCH subjects only waited the time it took to position the subject and equipment (5-10mins). When we compared data from the two centres however there was no significant difference in the % change from sitting to supine for any of the outcomes studied. We have assumed that this difference in supine time was not important, as the SCH cohort demonstrated no significant tendency to increasing LCI values with repeated measurements in the supine position. Another limitation of this study is that we predominantly studied CF children with mild lung disease, therefore the effects of posture change in more severe disease and in adult patients with CF is not known. We also did not randomise the order in which the subjects performed either sitting or supine MBW. Ideally the order would have been randomly assigned, however for both centres the MBW measurements were made as part of larger separate studies where sitting MBW was the primary outcome [10]. We can therefore not fully assess whether there was a learning effect from repeated MBW measurements.

Conclusion

We have demonstrated that children with CF and HC have an increase in LCI and a decrease in FRC when lying supine that is not simply due to changes in lung volumes. The change in LCI appears partly driven by an increase in Vt/FRC when supine and in HC may be the main factor contributing to this change in LCI. However, in CF subjects the changes in lung volumes can only explain a proportion of the change in LCI, which is also caused by true increases in ventilation heterogeneity. The effect of posture is hard to predict on an individual basis and care should be taken when correlating supine imaging measurements with physiology assessments performed seated.

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