Age and height dependence of lung clearance index and functional residual capacity

[1]Sooky Lum, [1]Janet Stocks, [1,2]Sanja Stanojevic, [3]Angie Wade, [1,4]Paul Robinson, [5]Per Gustafsson, [2]Meghan Brown, [1,6]Paul Aurora, [2]Padmaja Subbarao, [6]Ah-fong Hoo and [1]Samatha Sonnappa.

Online supplementary material

Multiple breath washout equipment

Pneumotachometer-transducer demodulator system

The flow meter used in this study was a pneumotachometer-transducer-demodulator system. The pneumotachometer (PNT) used in each centre is as shown in E Table 1. The PNT was connected to a Validyne variable pressure transducer (Model MP45-14-871, Validyne Corp, Northridge, USA) via equal lengths of stiff polyethylene tubing. The output from the pressure transducer was connected to a high gain carrier demodulator plug-in module which was part of a multi-channel modular transducer system. Prior to connection of the PNT, the transducer and demodulator were calibrated and balanced by use of an output voltmeter as recommended by the manufacturer.

Respiratory Mass spectrometer

The gas analysers used in all three centres were AMIS 2000 respiratory mass spectrometers (MS) (Innovision, Odense, Denmark). The dry concentrations of SF_6, He, CO_2, O_2 and N_2 in inspired and expired gas were measured continuously using the AMIS 2000 respiratory MS. The analogue flow and gas concentration signals were converted to digital signals using an A/D converter board in a personal computer, which sampled each channel at 100 Hz by use of custom-made software. Flow and gas signals were presented online during measurements.

The lag and response times of gas signals in relation to flow signals were measured using a method previously presented by Brunner et al [1]. The systems in the three centres were set up identically by Prof Per Gustafsson and the response time from 10 – 90% is 60 ms.

Sampling time for SF_6 was set at 10 ms and a cycling frequency of 33.3 Hz.

The **sampling rate** of the gases was 15 $mL.min^{-1}$

Signal to noise ratio: typically 200 but 100 or greater at 4% tracer gas was deemed acceptable.

Signal alignment: The signals were aligned by step response using a solenoid calibrated against the Brunner syringe method and automated within the data collection software.

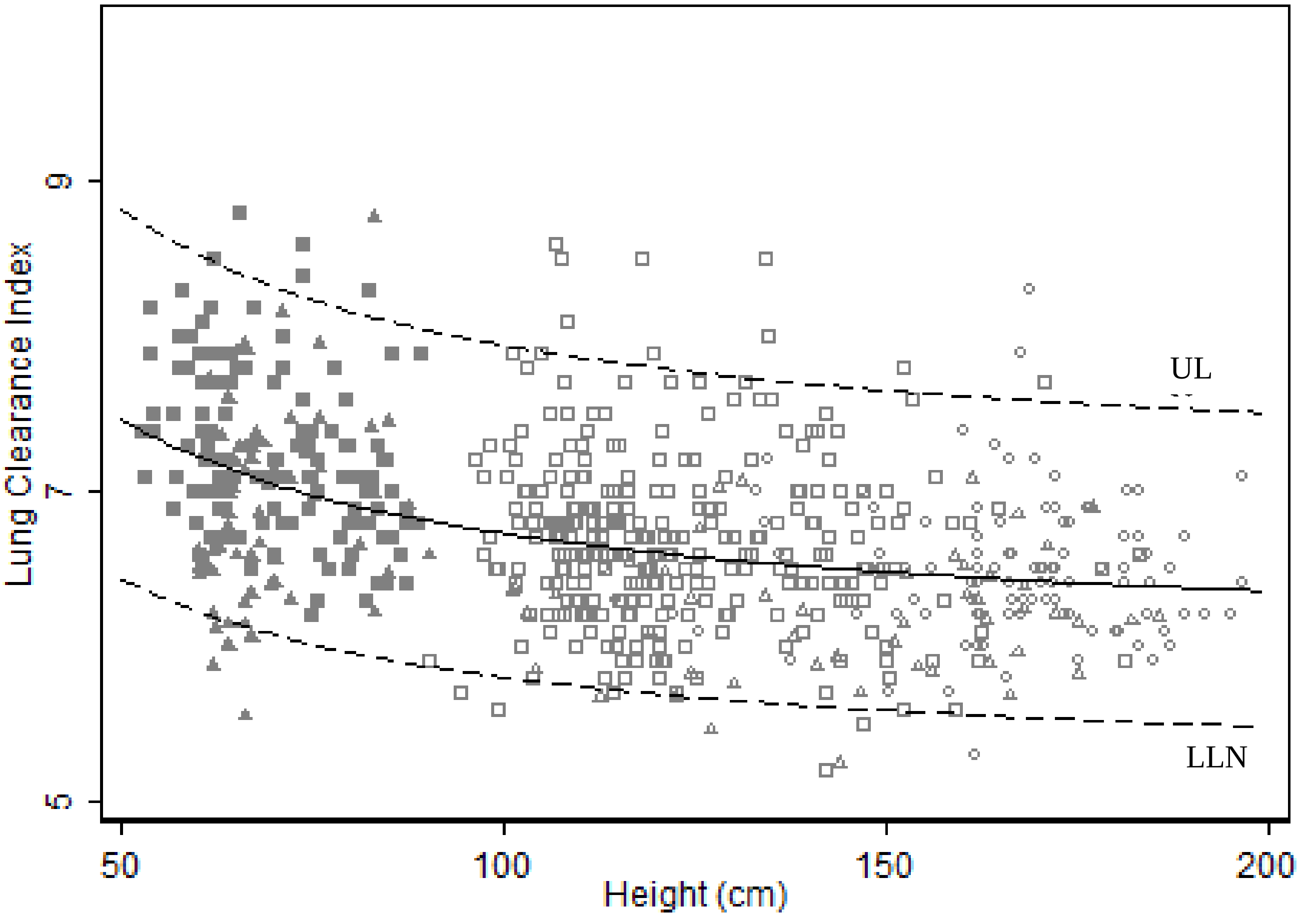
End tidal concentration (Cet) identification was undertaken using 5 samples, commencing with 4 samples before the end of expiration.

Table S1: Methodological differences between centres

	London, UK	**Skovde , Sweden**	**Toronto, Canada**
PNT type			
- Infant	Fleisch 0		Hans Rudolph 0-10L.min^{-1} (Age: <4 mo)
- PS and older	Fleisch 1	Fleisch 1	Hans Rudolph 0-35L.min^{-1}
Pre-capillary deadspace (mL)			
- Infant	<5kg: 5 ≥5kg: 7.5	- -	9.6
- PS	12.5	-	12.6
- SA	5	5	5
Post-capillary deadspace (mL)			
- Infant	5	-	10 (Age: <4 mo) 15 (Age: ≥ 4mo)
- PS	15	15	15
- SA	15	15	15

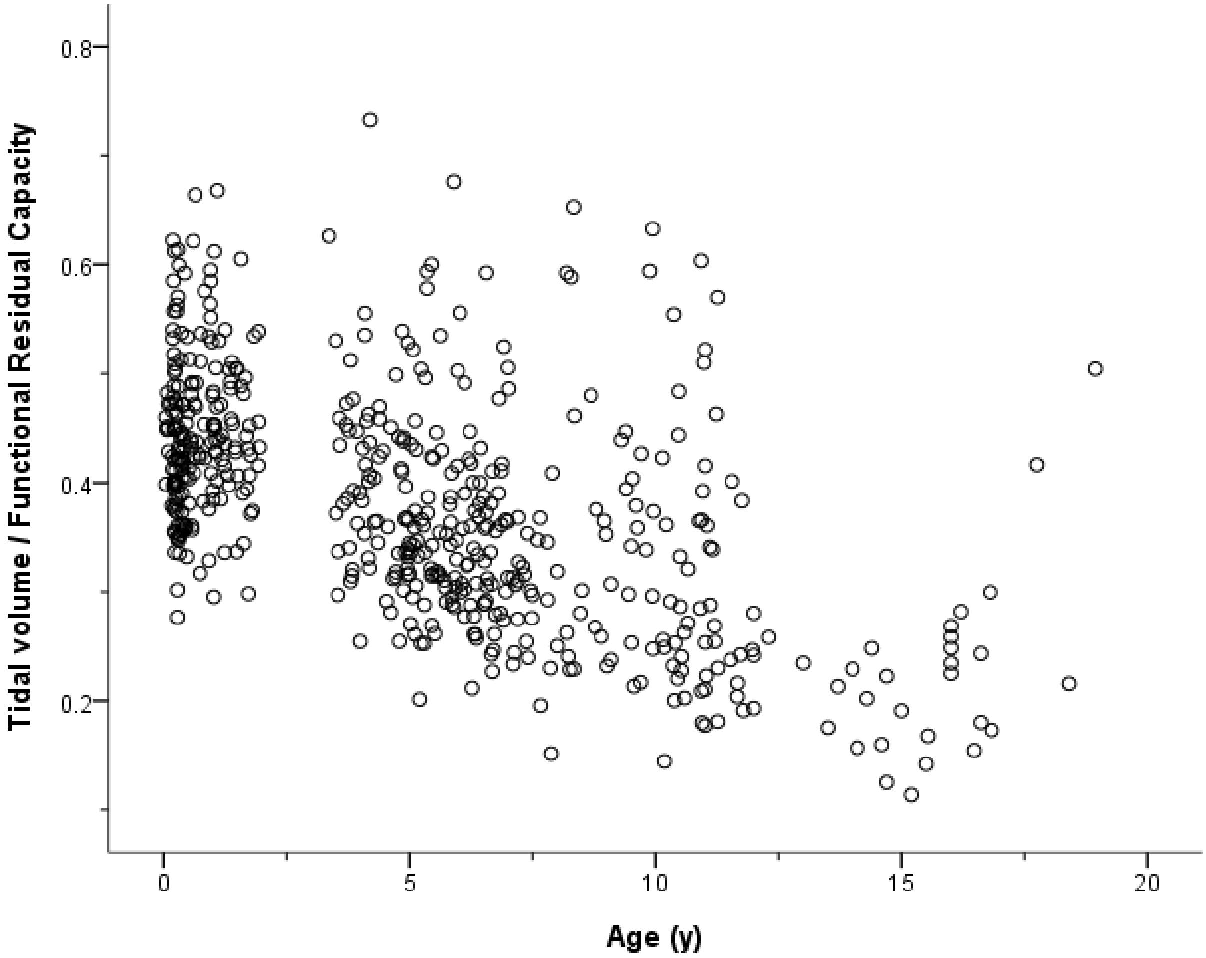
Results

Figure S1: LCI from infancy to 19 years if age according to centre and posture



Footnote: Solid line denotes the predicted (50th centile) LCI for height and the dashed lines denote the upper (ULN 97.5th centile) and the lower limits of the normal (LLN 2.5th centile) range.
Symbols: Square – London; Circle – Sweden; Triangle – Toronto; Closed – supine; Open – seated.
The graph above shows a continuous relationship between LCI and height across the age range including the transition from supine (closed symbols) to sitting (open symbols).

Figure S2:



Association between tidal volume/FRC$_{MBW}$ and LCI

As some data were collected over 10 years ago, the raw data were no longer accessible in one centre, thus VT data were only available in 281 subjects on 549 test occasions and the relationship between VT/FRC$_{MBW}$ and LCI could not be examined for the whole study population. As shown in E Fig 2, VT/FRC$_{MBW}$ was significantly related to age with younger subjects having a higher VT/FRC ratio compared to older subjects, reflecting differences in metabolism and developmental changes of the respiratory system of these younger subjects (E Figure 2, online supplement).

Table S2: Comparison of predicted FRC values obatined using Helium dilution and SF_6 MBW

Height (cm)	He Dilution (Stocks 1995)[2] Boys	(SF_6 MBW) Current study Boys	(He Dilution) (Stocks 1995)[2] Girls	(SF_6 MBW) Current study Girls
119	0.830	0.795	0.857	0.765
140	1.330	1.339	1.332	1.276
161	2.019	2.060	2.079	2.015

Predicted FRC presented in Litres

To compare predicted FRC between data collected using He dilution and the current study using SF_6 MBW, data from the current study were recalculated according to the height specified in the results reported by Stocks & Quanjer 1995. Interestingly despite different techniques and gases used, predicted FRC were fairly similar at each of the height ranges checked. However, this comparison is based on data from healthy children and may not be applicable to data from children with lung disease.

Analysis over-read

Over-read of an arbitrary sample of data selected from available datasets to encompass the entire paediatric age range (infants, pre-schoolers and school-age children) was undertaken by an independent observer (PR) who was not involved with data collection at any of the three sites.

Results

The over-read analysis, undertaken using a newer version of software, demonstrated that results were comparable between the original analysis and the over-read (2-3% mean difference for both LCI and FRCmbw) and that no inter-centre bias was observed.

Table S3: Paediatric reference equations for LCI and $\mathrm{FRC}_{\mathrm{MBW}}$

LCI	
L	**-0.8107**
M (Predicted)	**5.989+(73.851*height^{-1} [cm])**
S	**0.08**
ULN	**Predicted*((1.96*0.08*-0.8107) +1)$^{1/-0.8107}$**
FRC	
L	**0.2146**
M (Predicted)	**exp (-11.0665 +(2.1152*lnHeight) + (0.268*age$^{0.5}$ [y]) + (0.0445*sex))**
S	**exp(-1.689 + 159.612*height^{-2} [cm])**
ULN	**Predicted*((1.96*S*0.2146) +1)$^{1/0.2146}$**

Abbreviations: exp: exponential; lnHeight: natural log for Height; sex: boy = 1
*Footnote: Based on these equations, the ULN for LCI can be simplified to Predicted LCI * 1.182582; whereas that for* FRC_{MBW} *becomes (0.420616*S+1) to the power 4.659832 * Predicted FRC*

Sample size calculation for other devices

To calculate reference equations for other age groups and other devices, the sample size calculation will rely on the variability of the measurements, the range of patient characteristics in the sample (i.e. age/height) and the precision with which confidence intervals need to be estimated. For instance, halving the sample size would lead to confidence interval widths approximately 40% wider. Since the precision of reference equations is reduced at the extreme height ranges of the sample, where there are often fewer observations, the sample size should be uniform across the age range. Furthermore, to ensure the 2.5th and 97.5th centiles are as precise as the estimate of the mean, the required sample size needs to be 3 times that required for the mean estimate.

Reference List

1. Brunner JX, Wolff G, Cumming G, Langenstein H. Accurate measurement of N2 volumes during N2 washout requires dynamic adjustment of delay time. *J Appl Physiol* 1985; 59: 1008-1012.

2. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. *Eur Respir J* 1995; 8: 492-506.