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Original article

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Reference equations for tidal breathing parameters using structured light plethysmography

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Take home summary:

We have developed a set of reference equations for 7 key tidal breathing parameters measured using structured light plethysmography (SLP). We hope it helps clinicians better understand and interpret SLP data and the value of tidal breathing patterns.

Abstract

Tidal breathing measurements can be used to identify changes in respiratory status. Structured light plethysmography (SLP) is a non-contact tidal breathing measurement technique. Lack of reference equations for SLP parameters makes clinical decision-making difficult. We have developed a set of growth adjusted reference equations for seven clinically pertinent parameters of respiratory rate (RR), inspiratory time (Ti), expiratory time (Te), duty cycle (Ti/Total-breath-time), phase (thoraco-abdominal asynchrony or TAA), relative thoracic contribution (RTC) and IE50 (tidal inspiratory/expiratory flow at 50% volume).

Reference equations were developed based on a cohort of 198 seated healthy subjects (age 2-75 years, height 82cm-194cm, 108 Male). We adopted the same methodological approach as the global lung function initiative (GLI) report on spirometric reference equations [1]. Five minutes of tidal breathing was recorded per subject. Parameters were summarised with their medians. The online supplement provided is an integral part of this work and a reference range calculator is also provided therein.

We found predicted RR to decrease with age and height rapidly in the first 20 years and slowly thereafter. Expected Ti, Te and RTC followed the opposite trend. RTC was 6.7% higher in females. Duty cycle increased with age, peaked at 13 and decreased after. TAA was high and variable in early life and declined rapidly with age. Predicted IE50 was constant as it did not correlate with growth.

These reference ranges for seven key measures ensure clinicians and researchers can identify tidal breathing patterns in disease and better understand and interpret SLP and tidal breathing data.

Keywords: Structured light plethysmography, SLP, Normative value, reference range, reference equation, Respiratory rate, inspiratory time, expiratory time, thoraco-abdominal asynchrony, phase, relative contribution, IE50, duty cycle, tidal breathing, TAA

Introduction

Whilst spirometry is the cornerstone of traditional lung function assessment, it is not always possible to obtain reliable spirometry in patients who cannot perform the forced manoeuvres. There is also evidence that respiratory viruses can be transmitted in aerosols generated by asymptomatic individuals [2], especially during the forced manoeuvres of lung function tests [3]. Measurement of tidal breathing patterns are easier to perform, provides a complementary method to traditional lung function and breathing assessment in children and adults [4, 5] and minimises cross-infection risk.

Structured light plethysmography (SLP) is an established technique for non-contact measurement of respiratory motion [6–12]. A checkerboard pattern of light is projected onto the subject's thoraco-abdominal (TA) wall. Using two precisely angled cameras the three-dimensional coordinates of each intersection point on the checkerboard is determined and tracked over time. Displacement on the axis perpendicular to the surface of the TA wall can be spatially averaged over different regions [compartments] (e.g. chest and/or abdomen) to generate 1-dimensional compartment specific time-series (Figure 1). It is worth noting that some of the parameters studied here have been previously validated against tidal breathing data measured with a spirometer [6].

Figure 1. Working principle of SLP. The green trace corresponds to the thoracic movement, the blue trace shows the abdominal movement and the purple trace is the summation of blue and green traces, reflecting the movement of the entire thoraco-abdominal wall.

The pattern of tidal breathing can be derived from the displacement of the TA wall and a number of tidal breathing parameters can be calculated from this pattern. We report seven key tidal breathing parameters measured with SLP, respiratory rate (RR), inspiratory time (Ti), expiratory time (Te), duty cycle (Ti/Ttot), thoraco-abdominal asynchrony (TAA), relative thoracic contribution (RTC) and IE50 (tidal inspiratory/expiratory flow at 50% of tidal volume, IE50 is also a surrogate measure of airway obstruction [7]). The calculation of IE50 is not based on absolute flow and volume measurements, rather, it is derived from the movement of the TA wall (analogous to volume) and the first derivative of TA wall movement (analogouse to flow).

We provide a set of growth adjusted reference equations for these parameters. They were selected as they had shown clinical utility. Table 1 in the online supplement lists these parameters, their definitions, and their clinical utility. This is the first reference data of its kind, and the authors anticipate it will aid clinicians and researchers to better quantify, understand and interpret SLP data and tidal breathing patterns. The online supplement provided is an integral part of this study and it is highly recommened that readers who seek further detail consult it as they go through the study.

MATERIALS AND METHODS

Data

SLP data from clinical and research measurements collected from multiple sites (Queen Elizabeth [QE] Hospital, Birmingham, UK, Addenbrookes Hospital, Cambridge, UK, University Hospital North Midlands [UHNM], Stoke-on-Trent, UK) were collated retrospectively. Data collected from QE were control data for an alpha1-antitripsen deficiency study [13]. Data from Addenbrookes Hospital (Cambridge University Hospitals NHS Foundation Trust) were a mix of data for healthy and unhealthy subjects recruited for validation of SLP. Data from UHNM were control cohorts of two asthma studies in [7, 8]. All studies had been approved by their respective ethics committees and we obtained informed consent prior to data acquisition.

SLP data were captured using Thora-3Di (PneumaCare Limited, Cambridge, UK). Inclusion criteria were; subjects with no history of respiratory disease, who had 5 minutes of SLP capture in seated position and had a BMI<40. Subjects wore a taut white t-shirt (or the test was done on bare skin). In total, 73 data sets were excluded from the analysis details of which can be found in the online supplement (under the Data section). This left 198 clean SLP captures, each containing quiet tidal breathing (at rest) which passed the quality checks. The quality checking criteria for SLP signal is detailed under the SLP signal processing section in [9]. Parameters were summarised for each 5-

minute epoch by taking the median. Each data set was accompanied by subject age, sex, height, and weight. Ethnicity wasn't specified. None of the subjects were sedated for measurement. Age of subjects ranged from 2 to 75 years, height between 82cm to 194cm and weight between 14Kg to 149Kg. Further information on data quality assessment, exclusions and demographic information can be found in the online supplement under the Data section.

Statistical analyses

We adopted the same methodological approach as the GLI publication on spirometric normative equations [1]. GAMLSS (Generalised Additive Models for Location, Scale and Shape) package in R (version 3.5.2, www.r-project.org) was used to develop the reference equations [14]. GAMLSS is capable of modelling the expected value (μ, M or mean), coefficient of variation (sigma or σ) and skewness (lambda or λ) of a distribution. We assessed scatter plots of each parameter against age, height, weight, and sex to identify the regressors. Distribution of the dependent variable (e.g. RR, Ti, Te) was visualised using histograms. For each parameter various combinations of independent variables (e.g. age, height, weight, sex), their higher powers and their interactions were tested. Schwarz Bayesian criterion (SBC) was used to identify the most parsimonious model [15]. Normal Q-Q plots, worm plots [16] and visual assessment of the distribution of the residuals were done to ensure each fit was sufficiently representative. The model for each parameter and its considerations are detailed in the online supplement under the Equations section.

RESULTS

A SLP normative value calculator Excel spreadsheet was developed to facilitate calculation of reference ranges for the studied parameters. The calculator is colour coded to simulate a "traffic light" approach. It is also possible to manually input observed values for each parameter and automatically obtain their corresponding z-scores. The calculator spreadsheet is available in the online supplement. In the subsequent section, growth related trend for each parameter is depicted. The black line shows the expected or predicted value, the blue line is the upper limit of normal (ULN), and the green line is the lower limit of normal (LLN). Probability of observing a value lower than the LLN or higher than the ULN is 2.5%.

Respiratory rate

Figure 2 shows growth-related change in median RR. Height entries are estimated rather than observed (see the "Visual representation of the reference equations" section in the online supplement for more information), the graph provides only an approximate guidance on the overall trend, for actual values use the normative value calculator spreadsheet.

Figure 2. Growth-related changes in median RR.

Inspiratory time (Ti)

Figure 3 depicts the growth-related changes in median Ti. Inspiratory time increases rapidly during early life and up to approximately 20 (where the slope falls to 0.1) and almost linearly thereafter. Height entries are estimated and therefore the graph only provides a guidance on the overall trend.

Figure 3. Growth-related change in median Ti.

Expiratory time (Te)

The model for Te depends only on age, therefore, Figure 4 accurately depicts the age-related changes in median Te.

Figure 4. Growth-related change in median Te.

Duty cycle (Ti/Ttot)

Duty cycle increases during early life, peaks at 13 year and gradually decreases thereafter. Duty cycle is dependent on both age and height and therefore Figure 5 provides an approximate guidance on the overall trend.

Figure 5. Growth-related change in median duty cycle.

Relative thoracic contribution (RTC)

Figure 6 shows the age-related changes for RTC for males and females separately. RTC increases with age and is approximately 6.7% higher in females across all ages. Figure 6 can be used directly for interpretation as the model does not depend on height.

Figure 6. Growth-related change in median relative thoracic contribution (RTC). The dotted lines separate males from females.

Thoraco-abdominal asynchrony (TAA)

TAA was modelled with age only and as such Figure 7 can be used directly for interpretation. TAA is high and variable during early life and decreases considerably in both magnitude and variability with age.

Figure 7. Growth-related change in median thoraco-abdominal asynchrony (TAA).

IE50

Given the current sample size, IE50 does not appear to significantly correlate with age, height or sex. Therefore, the expected value and the upper and lower limits of normal are constant. Figure 8 provides a visual clarification for this.

Figure 2. IE50 does not correlate with age, height or sex. Expected value, LLN and ULN were respectively equal to 1.29, 0.96 and 1.88.

Discussion

This study, for the first time, provides a preliminary set of normative (reference) equations for seven tidal breathing parameters of respiratory rate (RR), inspiratory time (Ti), expiratory time (Te), duty cycle, thoraco-abdominal asynchrony (TAA), relative thoracic contribution (RTC) and IE50 measured by structured light plethysmography. Below we will discuss our findings regarding each parameter in relation to the existing body of literature.

Respiratory rate (RR)

Normative equations or reference ranges for RR have been covered in the literature for infants [17] and children 3 years old and younger by Gigliardi *et. al.*[18]. Gigliardi used body weight as the sole predictor of respiratory rate in 635 infants and children between 14Kg to 20Kg. These data are similar, with RR ranging from 18 to 35bpm (judging from the scatter plot labelled Figure 2) and between 18 and 32bpm and in our study.

For children 4 to 16 years old Wallis and colleagues [19] provide a set of normative equations based on direct measurement of RR by observing the movement of the chest in 1109 healthy resting children in seated position. The reported upper and lower limits of normal (i.e. upper and lower 2.5%) are narrower than in our study here.

Our expected values and trend of changing respiratory rate with age also agrees with a review article providing reference equation for RR in the first 18 years of life. Fleming *et. al.* [20] reported a rapid reduction in respiratory rate and its variability most pronounced during early life, particularly in the 2-3 year olds.

In adults, the norm seems to be a constant 12-20bpm range for RR [21]. Looking at the entire age range, our results suggest a more rapid decline in approximately the first 20 years of life and a small linear reduction thereafter. The reported expected values for adults are well within the suggested range potentially indicating an agreement.

Inspiratory time (Ti), expiratory time (Te) and duty cycle (Ti/Ttot)

Normative values or reference equations are not well established for Ti and Te during quiet tidal breathing. Most studies pertain to mechanical ventilation. Indications of what might constitute a normal Ti and Ti/Ttot however do exist. Tobin *et. al.*[22] report a normal Ti of 1.6±0.3 seconds in young (20 to 50years, N_{young}=47) and 1.67±0.35 seconds in older (60 to 81years,N_{old}=18) healthy subjects. Note that the reported values are mean and standard deviation measured in the supine position. The average age for the young and old cohorts were 29 and 69 year respectively. Using our equation to calculate Ti by substituting 29 for age and the predicted height from our data (≈174cm), the predicted value was 1.54 seconds. For a 69 year old with estimated height of approximately 170cm, the predicted Ti was 1.59 seconds. This is a crude comparison and the discrepencies can be attributed to different measurement devices (SLP vs. RIP), subject position (seated vs. supine), summary statistic (median vs. mean) and possibly to a different demographic. The trend and the difference between old and young cohorts is however confirmed in our data. We found that Ti increases with age and height up until approximately 20 years of life and more slowly thereafter

Expiratory time (Te) is similar to Ti. There are few published studies looking at normative expiratory time in tidal breathing in healthy subjects. Those published do not overlap with the age range investigated in this study. In short, our results suggest that Te increases more rapidly during the first 20 years of life and gradually (linearly) thereafter.

Duty cycle (Ti/Ttot) has also been primarily used in relation to mechanical ventilation [23]. We have observed an increase in duty cycle in children up to 13 years and a gradual decrease with age thereafter. Parriera *et. al.* [24] measured Ti/Ttot in 104 healthy subjects in the supine position using calibrated RIP bands. They reported a significant difference between males and females in the younger cohort (20 to 39 years) but not in the other age bands. In our equation for Ti/Ttot, sex has not been identified as a determining factor (Ti/Ttot was predicted by age and height only). Mendes *et. al.* [25] using Optoelectronic plethysmography with 83 healthy adult subjects, report that Ti/Ttot did not change with posture or sex which confirms our finding. Furthermore, actual values reported for expected Ti/Ttot in healthy adults are broadly similar to ours, with Tobin [22] and Parreira [25] reporting an average Ti/Ttot of approximately 0.42±0.03 and 0.39±0.04 respecitvely. Wilkens *et. al.* [26] report an average duty cycle of 0.37 in 10 healthy adults at rest using OEP which appears to be lower than our estimated expected value for similar age and height though this difference might be explained by the small sample size (10 vs 198) and use of an alternative summary statsitic (mean vs median).There are no published normative values of Ti/Ttot for children and therefore our study here provides this unique data.

Thoraco-abdominal asynchrony (TAA)

Phase angle or thoracoabdominal asynchrony (TAA) has been used to assess respiratory function in children [7, 8, 27] and adults [9, 28]. Based on our data, TAA is high and variable during early life and reduces in both magnitude and variability with age. Mayer *et. al.* [29] report an average TAA of 15.7 degrees in a cohort of 50 young children (3-5 years old) in the seated position. This agrees with our results, as does the apparent trend of decreasing TAA with age (see Figure 7 in [29]). Parreira *et.al.* [24] report phase angle in adults, but the reported values are considerably higher than ours (approximately 5 vs 13 degrees). This is likely due to the difference in position of subjects (supine vs seated). A higher TAA in supine position compared to seated is shown in [29]. TAA in healthy subjects in seated position is also reported in [28, 30]. The number of healthy subjects is low (10 and 9 at rest respectively), and the method for calculation of phase differs slightly from what we have used here. The reported values for phase in these studies can take either a negative or positive number whereas in our study TAA is an absolute measure of asynchrony (a non-negative number) [27]. Looking at the absolute values of the reported TAA in healthy subjects at rest, we see a rough agreement with our results here (low TAA in adult subjects, generally around 5 degrees and not exceeding 10 degrees).

Relative thoracic contribution (RTC)

Relative thoracic contribution characterises the spatial dynamics of the thoraco-abdominal motion. This parameter has been studied in monitoring of several patient groups; post thoracic surgery [31], neuromuscular disease [10], dysfunctional breathing [32], COPD [33] and in weaning patients from mechanical ventilators [34]. In our study, we have found that RTC increases with age and is approximately 6.7% higher in females than in males across all ages included in the study. Our results partially fit with Mendes' [25] account of ribcage contribution when it comes to females having a higher ribcage contribution, but differs in the reported trend of decreasing ribcage contribution with age in adults subjects, seen in Mendes' and other studies [35]. In infants and very young children the trend seems to be the opposite, with RTC increasing with age [36]. A comparison between reported values for RTC in children [37] and adults [25] also indicates that ribcage contribution may increase from childhood to adulthood and that is where we have seen the most pronouced increase in our study. Reported values for ribcage contribution seem to be inconsistent [25, 37, 38] but most studies agree that RTC is higher in females and that ribcage contribution decreases with age in healthy seated adults. We speculate that this descripancy may be due to inclusion of both children and adults in determining the reference equation. Additionally, our study has the largest sample size in comparison to aformentioned studies which may carry with it deeper insight.

IE50

IE50 is as defined by Kaplan *et. al.* [39] and is not studied as extensively as some of the other tidal breathing parameters and as such published normative values or reference equations for IE50 are currently unknown. As a surrogate measure of airway obstruction [7] it quantifies the effective shape of tidal breathing flow/volume (TBFV) loop at the middle point (tidal volume =50%), IE50 was not found to correlate with age, sex or height in our study, therefore its expected value (1.29) and upper and lower limits of normal (0.96 and 1.88 respectively) remained constant across the population.

Limitations

The sample size could be criticised for a normative value study. However, it should be emphasised that SLP is still novel and as such a large volume of data is yet to be collected. Interest in SLP is growing, and new data will augment the data sets presented. Although a sample size of 198 is not representative of an entire population, distribution analysis of the parameters allowed accurate modelling of the predictive equations. Our recent small-scale clinical validation of the developed reference equations also confirms this and shows promise [40]. More information on the validation study can also be found in final section of the online supplement. This is an extremely valuable starting point for interpretation of breathing pattern data as evidenced in the discussion, as well as for SLP.

Another shortcoming of the study was in recruitment of healthy subjects which was based on having no history of a respiratory disease. It would have been ideal to have basic spirometry and smoking history available. In addition, since ethnicity data was not recorded, reference equations were not adjusted for ethnicity.

Conclusion

We have provided a set of growth adjusted reference equations for seven tidal breathing parameters measured using structured light plethysmography. Expected normative values for respiratory rate (RR), inspiratory time (Ti), duty cycle (Ti/Ttot), and thoraco-abdominal asynchrony (TAA) agree well with previous studies.

Relative thoracic contribution (RTC) in females was higher than in males which is inline with the existing literature. The increasing trend of adult RTC with age in our study though contradicts the commonly reported reduction with age. We suspect this is due to inclusion of both children and adult subjects in our models. Expected values for normal RTC though as a whole remain inconsistent in the literature.

We have unique normative values for expiratory time and IE50. These equations may facilitate further use of these parameters in future research and clinical necessity.

A reference range calculator (an Excel spreadsheet) is provided in the online supplement which should help clinicians and researchers better interpret SLP data and tidal breathing in general. This may be of particular benefit given the COVID 19 pandemic since tidal breathing may be a non-AGP aleternative to lung function assessment.

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Figure 1

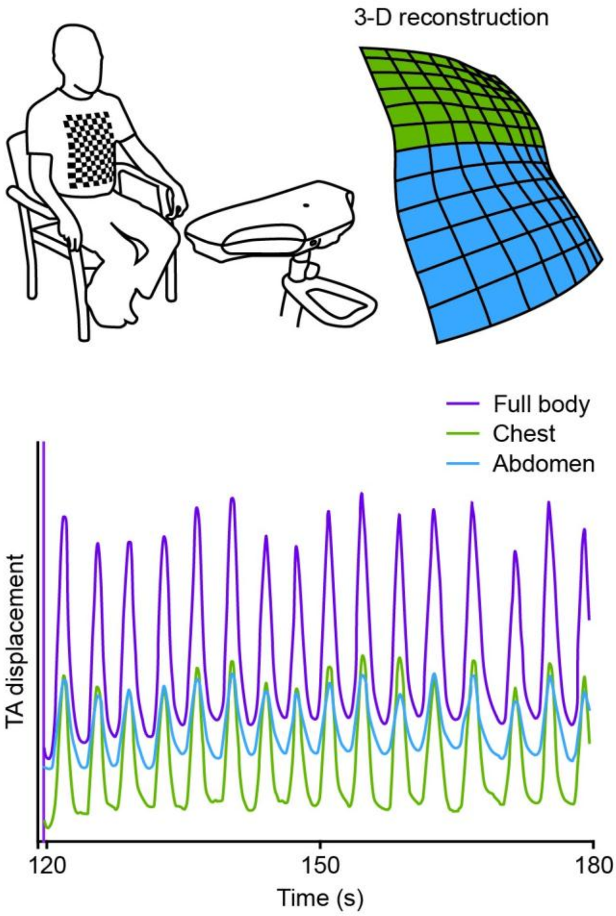

3-D reconstruction
Full body
Chest
Abdomen
TA displacement
120
150
180
Time (s)

Figure 2

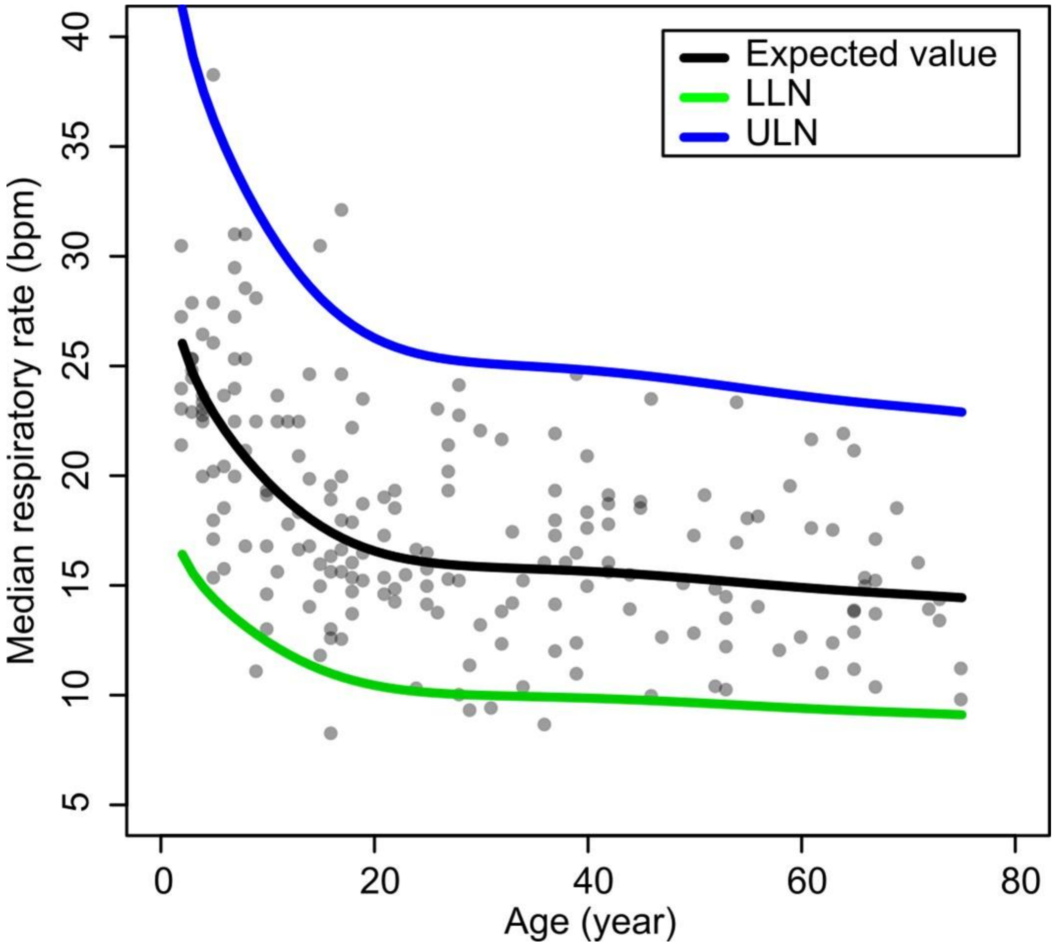
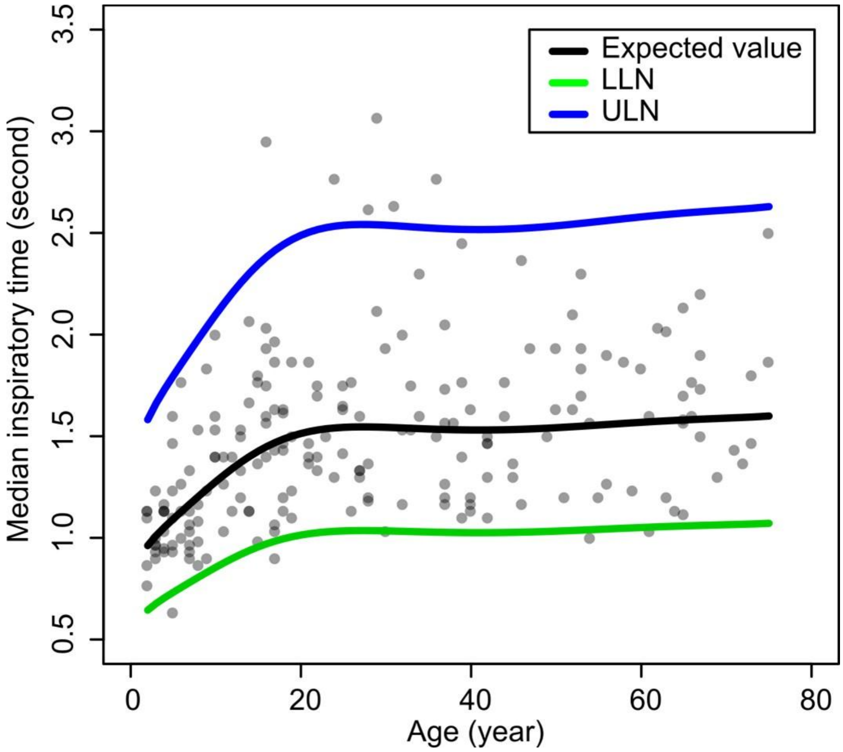

Expected value
LLN
ULN
Median respiratory rate (bpm)
Age (year)
5
10
15
20
25
30
35
40
0
20
40
60
80

Figure 3



Expected value
LLN
ULN
Median inspiratory time (second)
Age (year)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0
20
40
60
80

Figure 4

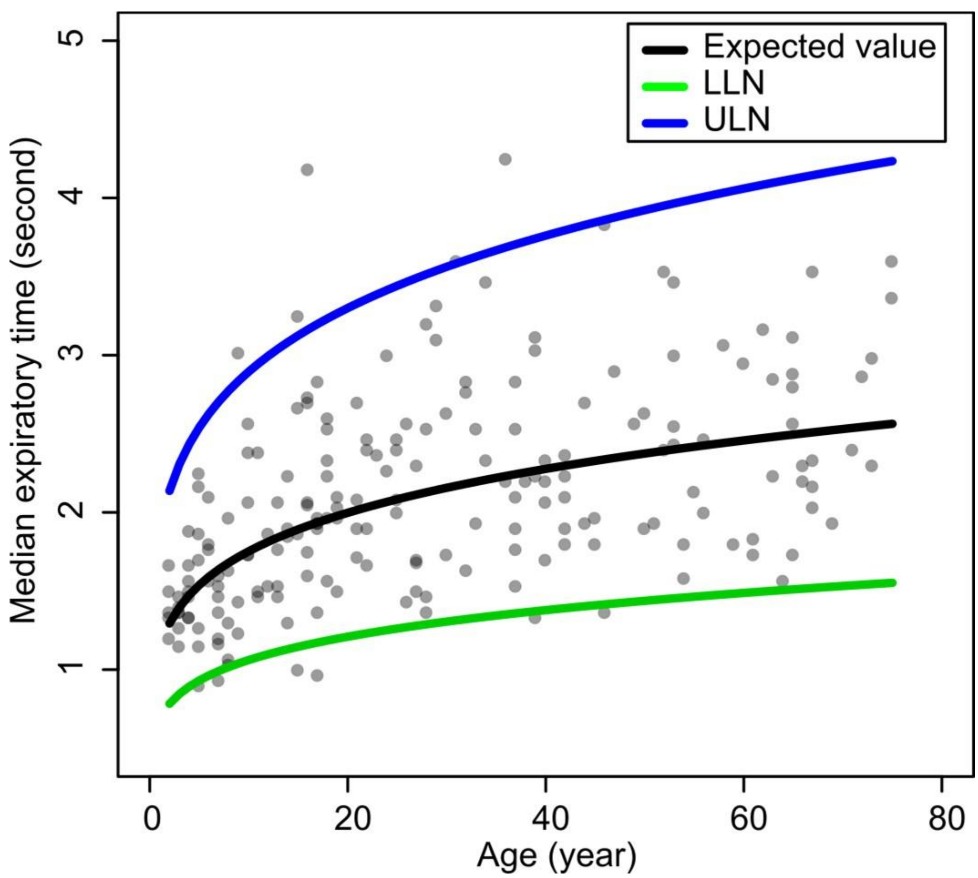
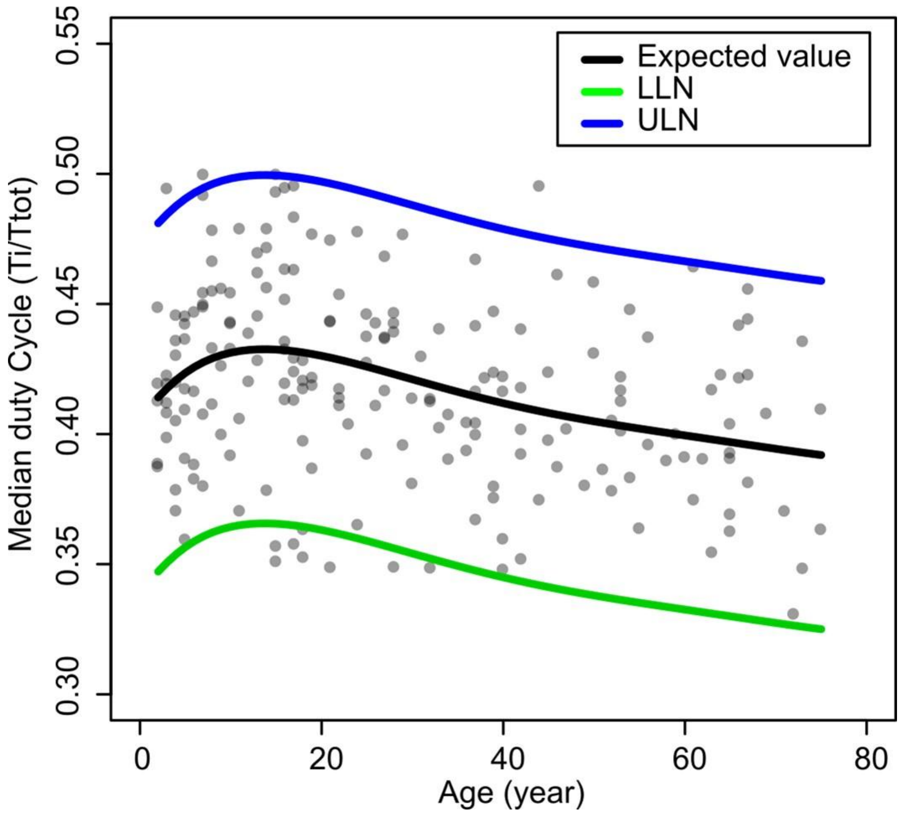
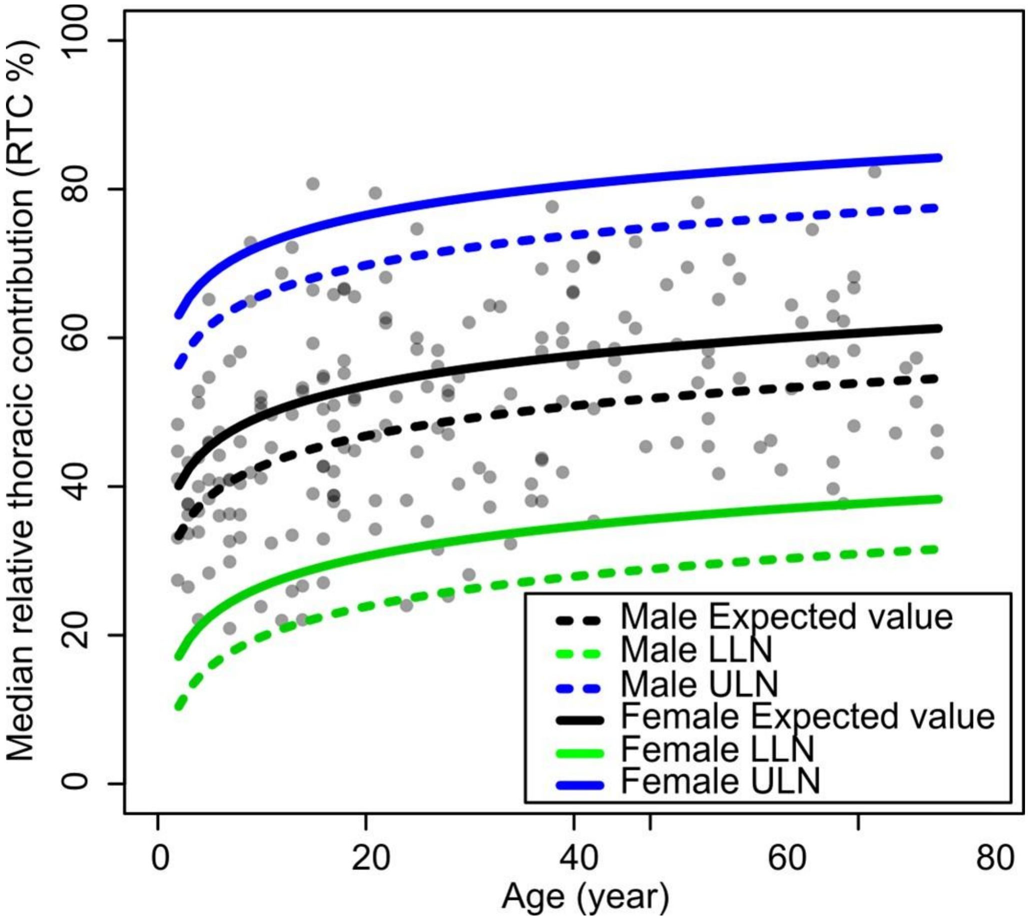

Expected value
LLN
ULN
Median expiratory time (second)
Age (year)
1
2
3
4
5
0
20
40
60
80

Figure 5



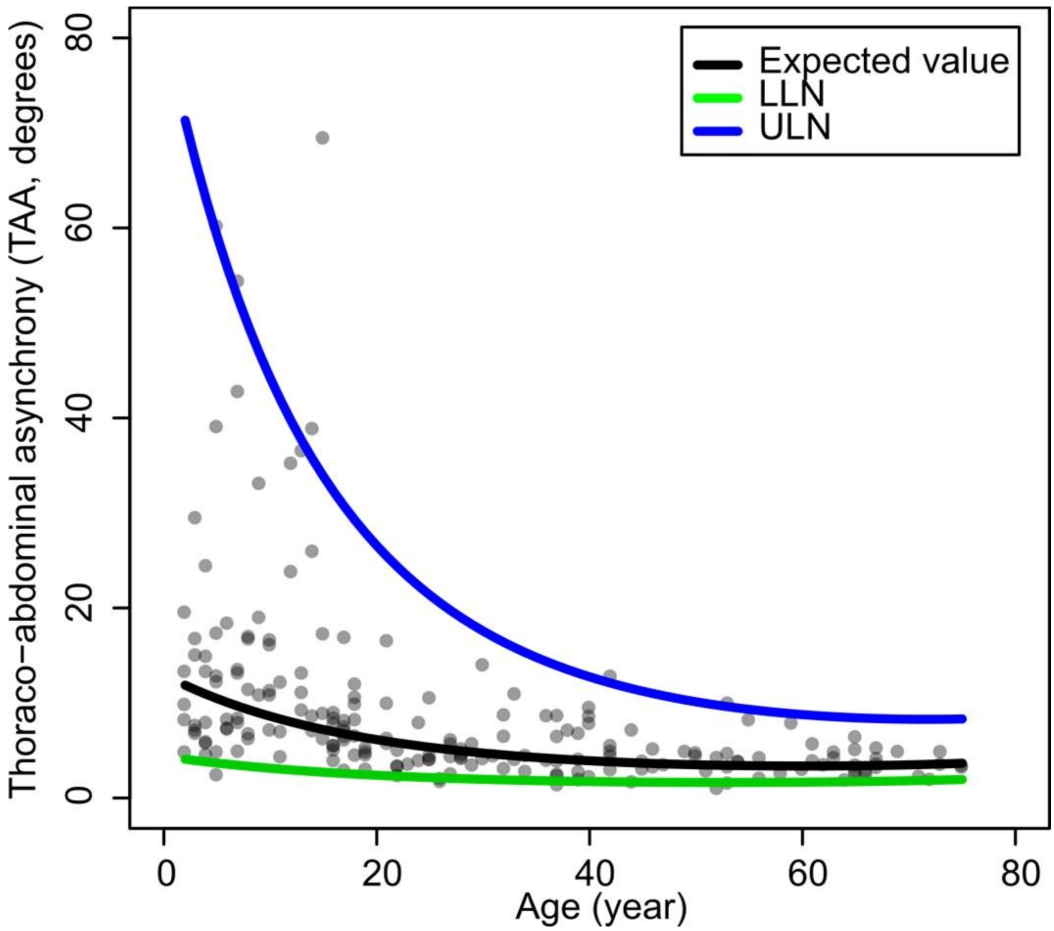
Expected value
LLN
ULN
Median duty Cycle (Ti/Ttot)
0.55
0.50
0.45
0.40
0.35
0.30
0
20
40
60
80
Age (year)

Figure 6



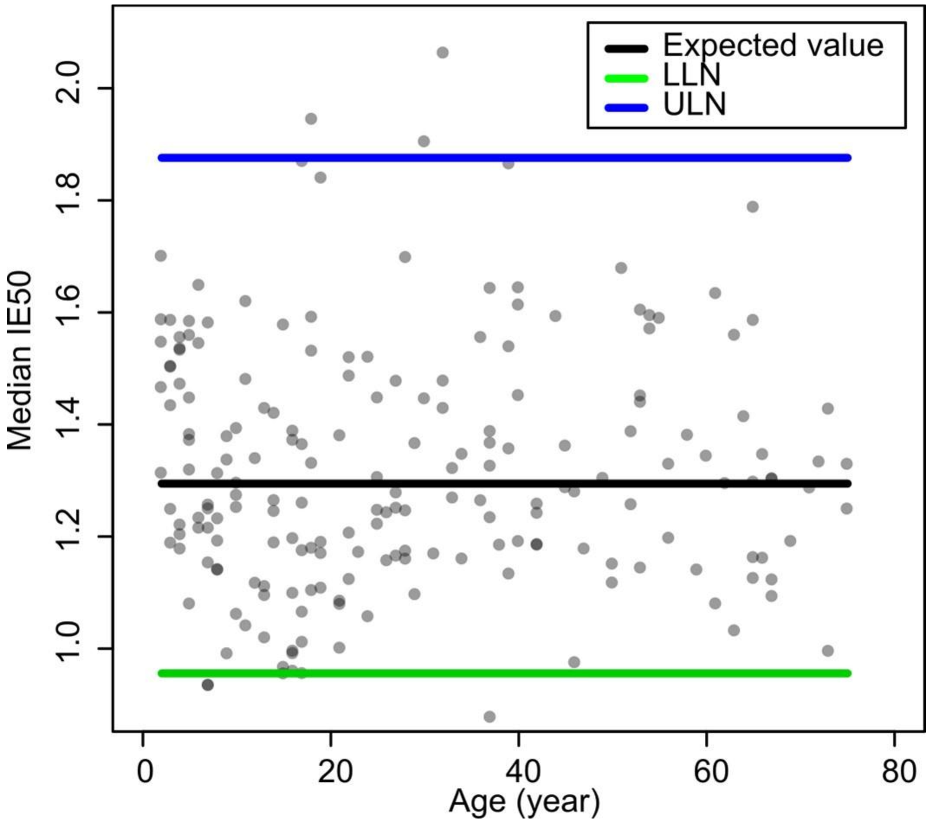
Median relative thoracic contribution (RTC %)
0
20
40
60
80
100
0
20
40
60
80
Age (year)
Male Expected value
Male LLN
Male ULN
Female Expected value
Female LLN
Female ULN

Figure 7



Expected value
LLN
ULN
Thoraco-abdominal asynchrony (TAA, degrees)
0
20
40
60
80
0
20
40
60
80
Age (year)

Figure 8


Expected value
LLN
ULN
Median IE50
2.0
1.8
1.6
1.4
1.2
1.0
0
20
40
60
80
Age (year)

Tidal breathing parameter description

Table 1. List of the 7 key SLP parameters addressed in the study, their definitions, abbreviations, and clinical utility

Tidal breathing parameter	Acronym	Definition	Relevant references
Respiratory rate	RR	Rate of respiration measured in breaths per minute (brpm), calculated as 60/total-breath-time	Definition and illustration [1], clinical importance of RR [2], validation of SLP generated RR against the gold standard [3]
Inspiratory time	Ti	Time in seconds that takes to inhale (calculated as the time interval between a trough on the full body respiratory signal [see Figure 1] and its proceeding peak)	Definition and illustration [1],validation of SLP generated Ti against the gold standard [3], Ti is shorter in COPD [4], Ti was shorter in children with acute asthma [5]
Expiratory time	Te	Time in seconds that takes to exhale (calculated as the time interval between a peak on the full body respiratory signal [see Figure 1] and its proceeding trough)	Definition and illustration [1], validation of SLP generated Te against the gold standard [3], Te was shorter in children with acute asthma [5]
Duty cycle	Ti/Ttot	Inspiratory time divided (normalised) by total-breath-time (unit-less parameter)	Definition and illustration [1], Ti/Ttot is lower in children with managed asthma [6], Ti/Ttot was lower in COPD [4]
Thoraco-abdominal asynchrony (also known as Phase or breath phase)	TAA	Phase measured in degrees indicating how synchronous chest and abdomen are moving together, based on the work of Konno and Mead [7]	Illustration and calculation [6, 8], TAA was higher in children with acute asthma [5], was higher in COPD [4]
Relative thoracic contribution	RTC	Relative contribution of thorax to entire thoraco-abdominal (TA) wall motion, calculated by dividing the peak-to-peak amplitude of thoracic movementby that of the TA wall movement	Illustration and calculation [6], reduced abdominal contribution in neuromuscular disorder [9], monitoring patients post lung resection surgry [10]
IE50	IE50	Quantifies the shape of tidal breathing flow-volume loop at tidal volume=50%. Tidal inspiratory flow at 50% (TIF50) divided by tidal expiratory flow at 50% (TEF50). It is a surrogate measure of airway obstruction. Note that with SLP it is calculated from the displacement of TA wall and its rate of change rather than volume and flow.	Definition and illustration [1, 4], it was high in COPD [4], it was high in children with managed and acute asthma [5, 6]

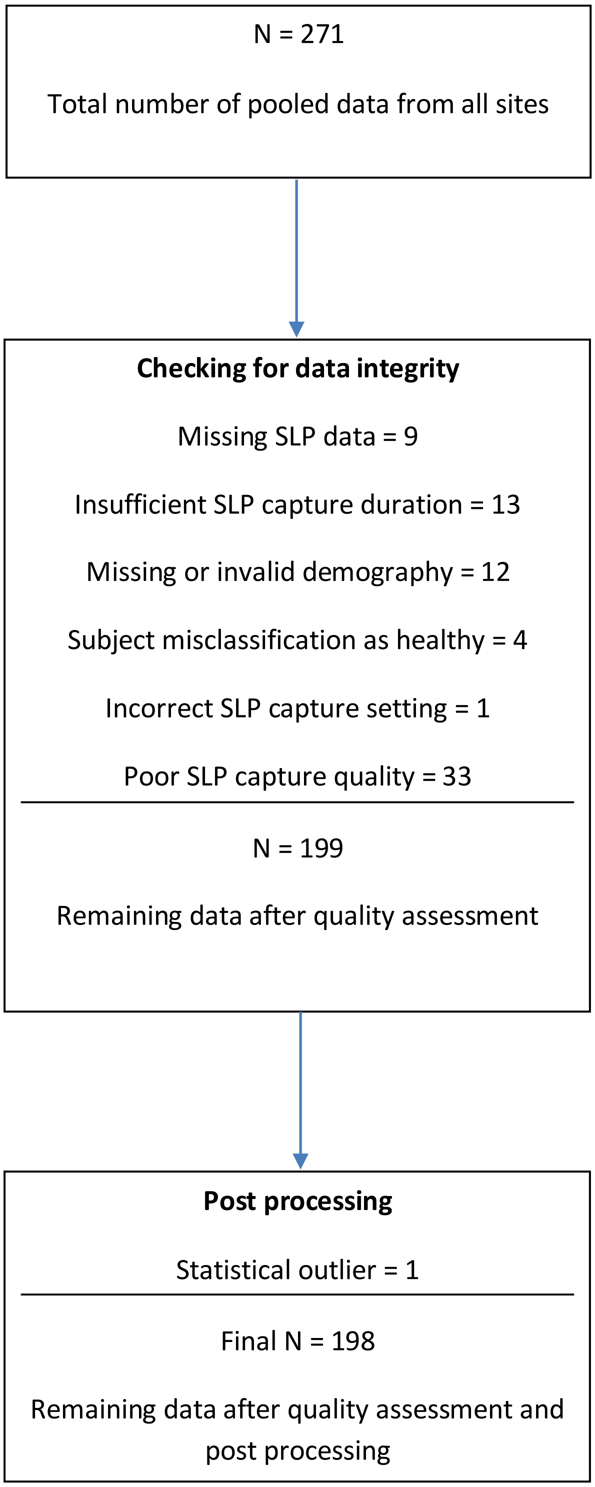
Data

Initially data from 271 subjects were pooled together (all in seated position). Case Report Forms (CRFs) were verified where possible to ensure entries were accurate. Data from SLP captures were individually assessed by one of the authors (SMF) for adequate quality. The quality checking criteria for SLP signal is detailed under the SLP signal processing section of the following article [4].Of the 271 pooled datasets, 13 were found to have less than 5 minutes of SLP data, 33 had poor quality (due to movement artefacts, lighting related artefacts, creases on the t-shirt, software/hardware malfunction), 12 had missing or invalid demographic entries, 4 had been misclassified as normal (as CRFs indicated), and for 9 subjects we were unable to find the corresponding SLP captures. Additionally, CRF notes for a 2-year-old indicated that the scan was taken as the child was sat on his mother's lap and as such the data was not deemed representative of the subject's breathing pattern. One final subject was removed as a statistical outlier (expiratory time>7 seconds, approximately 6 standard deviations away from the mean). Flow chart 1 below summarises this process. SLP data captures from younger subjects (who may not be able to sit still for 5 minutes) were assisted by showing them an age appropriate children's cartoon if necessary. Table 2 provides a breakdown of demographic information.

Age bands	N	Sex	Height Median [Min,Max]
2-5	25	17M:8F	97.0 [82.0,116.7]
6-9	19	9M:10F	126.5 [110.0,148.0]
10-13	14	7M:7F	150.8 [135.5,158.2]
14-18	28	14M:14F	167.9 [155.0,186.4]
19-25	19	13M:6F	182.0 [155.0,194.0]
26-35	22	13M:9F	173.0 [158.0,186.0]
36-45	26	10M:16F	164.5 [149.0,189.0]
46-55	16	8M:8F	171.5 [152.0,188.0]
56-65	16	8M:8F	167.0 [155.0,185.0]
66-75	13	9M:4F	173.0 [152.0,185.0]

Table 2. Demographic breakdown of the 198 healthy subjects

Flow chart 1. Summary of the data quality assessment procedure



Equations

Respiratory rate

Histogram of median RR and its scatter plots against age, height and weight were plotted. A logarithmic transform was done to normalise the distribution of median RR. The modelling procedure started with regressing logarithmically transformed RR on age:

$$ln(RR) = a + b \times Age$$

A number of different models were produced by alternating between several smoothers (cubic splines with degrees of freedom ranging from 0 to 3 and penalised beta spline [function pb() in the GAMLSS package]). Fractional polynomials with the number of polynomial terms ranging from 1 to 3 were also tested to identify the most parsimonious model. A single term fractional polynomial transform with power = 0 minimised the SBC. Note that the GAMLSS package logarithmically transforms the independent variable when power = 0. We repeated the above procedure with height as the independent variable, but the SBCs were not decreased any further. We then added height to the model. A single term fractional polynomial transform for height (power = 3) minimised the SBC. The final value of SBC was 9.92. Adding sex to the model did not improve the fit. The final model for RR therefore took the following form:

$$ln(RR) = a + b \times ln(Age) + c \times Height^3$$

Where *ln* is the natural logarithm and *a*,*b*, and *c*, are the coefficients of the model. Distrubtion of the tranformed RR was normal. Sigma remained constant (did not change with age or height suggesting that variability of RR is constant and does not change with age or height). Adding an interaction term to the model did not reduce the SBC. The following equation was used to determine predicted RR:

$$RR_{Predicted} = exp(a + b \times ln(Age) + c \times Height^3)$$

Where a=3.365, b= -0.114 and c= -4.105e-8 for every age and height entry. Note that strictly speaking, age range is limited to 2 to 75 years and height can vary only between 82cm and 194cm.

Upper and lower limits of normal (upper and lower 2.5%) were calculated using the following two euqations:

$$ULN_{RR} = 1.96 \times \sigma + RR_{Predicted}$$

$$LLN_{RR} = -1.96 \times \sigma + RR_{Predicted}$$

Where σ is constant and equal to 0.235. Upper and lower 2.5% cut offs for a standard normal distribution are approximated by 1.96 and -1.96 respectively, i.e. Pr(Z>1.96) = 2.5% and Pr(Z<-1.96) = 2.5% Where Pr denotes probability and Z is the standard normal distribution.

Inspiratory time

Age and height were identified as the most siginificant regressors. Similar to the previous model, a number of altenative smoothers were used for both independent variables. Ultimately, both height and age were transformed using a single term fractional polynomial (power = 3 and 0 respectively) which gave the following form for the normative equation (final SBC = 141.2):

$$Ti_{Predicted} = a + b \times Height^3 + c \times ln(Age)$$

Note that distribution of median Ti was not normal. A BCCG (Box-Cox-Cole-Green) distribution [11] for Ti with constant terms for coefficient of variation (sigma) and skewness (lambda) minimised the SBC. The calculated coefficients were a = 0.853, b = 7.76e-8, c= 0.084, sigma (σ) = 0.225 and lambda (λ) = -0.483. The BCCG distribution can be reconstructed using the above coefficients. Further information on distributions used in GAMLSS modelling can be found in [12]. The upper and lower limits of normal are given as follows (upper and lower 2.5%):

$$ULN_{Ti} = Ti_{Predicted} \times (\lambda \times \sigma \times (1.96) + 1)^{(\frac{1}{\lambda})}$$

$$LLN_{Ti} = Ti_{Predicted} \times (\lambda \times \sigma \times (-1.96) + 1)^{(\frac{1}{\lambda})}$$

Expiratory time

Median expiratory time (Te) was not normally distributed but a logarithmic transform normalised the distribution. Age was transformed with single term fractional polynomial (power=0) and was identified as the most significant regressor as the addition of height, weight or sex to the model did not reduce the SBC further (final SBC = 38.3). This gave the following form for the Te normative equation:

$$Te_{Predicted} = exp(a + b \times ln(Age))$$

Where a=0.127 and b=0.189 and Sigma (σ)=0.256. The LLN and ULN were calculated as follows:

$$ULN_{Te} = exp(ln(Te_{Predicted}) + 1.96 \times \sigma)$$

$$LLN_{Te} = exp(ln(Te_{Predicted}) - 1.96 \times \sigma)$$

Duty cycle (Ti/Ttot)

Median Ti/Ttot (duty cycle) was initially found to best follow a BCCG distribution. With further inspection, we found a simpler model with nearly identical fit which increased the SBC by 1 point. In the interest of simplicity the latter model was adopted (SBC = -754.2). In this model median Ti/Ttot follows a normal distribution with age and height as predictors. Age and height were tranformed using a single term fractional polynomial with power equal to 0.5 and -0.5 respectively. This gave the following equation:

$$Ti/Ttot_{Predicted} = a + b \times Age^{0.5} + c \times Height^{-0.5}$$

Where median Ti/Ttot followed a normal distribution with $Ti/Ttot_{Predicted}$ as mean and σ as the standard deviation. The coefficients were calculated to be the following a=0.572, b=0.009, c=-1.361 and σ=0.034. The upper and lower limits of normal were calculated as follows:

$$ULN_{Ti/Ttot} = 1.96 \times \sigma + Ti/Ttot_{Predicted}$$

$$LLN_{Ti/Ttot} = -1.96 \times \sigma + Ti/Ttot_{Predicted}$$

Relative thoracic contribution (RTC)

Median relative thoracic contribution followed a normal distribution and was predicted by logarithmically transformed age and gender. The normative equation for median relative thoracic contribution to total thoraco-abdominal movement has the following form (final SBC = 1557.5):

$$RTC_{Predicted} = a + b \times ln(Age) + c \times Gender$$

Gender is a binary categorical variable with (F for female and M for male). The coefficients for the model were a=36.05, b=5.839, c=-6.734 and the σ of the normal distribution was 11.714. There were no interactions between age and gender suggesting that there was a constant difference between RTC in males and females with females having an approximately 6.7% higher RTC. Upper and lower limits of normal were calculated as follows:

$$ULN_{RTC} = 1.96 \times \sigma + RTC_{Predicted}$$

$$LLN_{RTC} = -1.96 \times \sigma + RTC_{Predicted}$$

Thoraco-abdominal asynchrony (TAA)

Thoraco-abdominal asynchrony (TAA) is one of the pivotal parameters in tidal breathing analysis. TAA is high in young children and rapidly declines with growth. A generalised Gamma distribution was found to adequately describe the pattern of median TAA. Expected value of median TAA was predicted by age and age squared. Sigma of the distribution varied with age and lambda was a constant. The equation for expected value of median TAA therefore took the following form (final SBC = 1097.4):

$$TAA_{Predicted} = exp(a_{\mu} + b_{\mu} \times Age + c_{\mu} \times Age^2)$$

Note that the GG distribution in Gamlss uses a log-link for the mu (expected value) hence the exponentiation. The coefficients of the model for predicted TAA were a_{μ}=2.562, b_{μ}=-0.045 and c_{μ}=0.0004. The equation for sigma of the distribution was the follwing:

$$TAA_{\sigma} = exp(a_{\sigma} + b_{\sigma} \times Age)$$

Where a_{σ}=-0.363 and b_{σ}=-0.009. Similar to the expected value equation, the exponentiation is here to adjust for the log-link used in the GG distribution for sigma. Lambda was constanst and equal to λ=-.075. ULN and LLN can be calculated using the inverse of the gamma cumulative distribution function. We denote the inverse of the cumulative gamma distribution by F^{-1}(p,α,β) where p is the probability, α is the shape parameter and β is the scale parameter. ULN and LLN are then given by the following:

$$ULN_{TAA} = TAA_{Predicted} \times (F^{-1}(0.975, \alpha, \beta))^{\frac{1}{\lambda}}$$

$$LLN_{TAA} = TAA_{Predicted} \times (F^{-1}(0.025, \alpha, \beta))^{\frac{1}{\lambda}}$$

Where $\alpha = \frac{1}{\lambda^2 TAA_{\sigma}{}^2}$ and $\beta = \lambda^2 TAA_{\sigma}{}^2$.

IE50

IE50 is another pivotal parameter in SLP tidal breathing analysis. IE50 is a surrogate measure of airway obstruction. Median IE50 did not change significantly with age, height or sex. A BCCG distribution was found to adequately fit the distribution of median IE50 (no predictors). Parameters of the distribution were (final SBC = -22.2):

$$IE50_{Predicted} = 1.294$$

$$IE50_{\sigma} = 0.17$$

$$IE50_{\lambda} = -0.6$$

$IE50_{Predicted}$ is the expected value or µ. For further information on GAMLSS distributions see [12]. The ULN and LLN are calculated as follows:

$$ULN_{IE50} = IE50_{Predicted} \times (IE50_{\lambda} \times IE50_{\sigma} \times (1.96) + 1)^{\frac{1}{IE50_{\lambda}}}$$

$$LLN_{IE50} = IE50_{Predicted} \times (IE50_{\lambda} \times IE50_{\sigma} \times (-1.96) + 1)^{\frac{1}{IE50_{\lambda}}}$$

Screenshot of the SLP normative value calculator

Please Insert Subject Details in the ENTER Column

SLP parameters (observed) are obtained from the PneumaView 3D software

SLP reference ranges are based on 198 measurements on seated normal subjects (no history or respiratory disease).

Subject Info		**SLP Parameter**	**Observed (measured)**	**Expected value (predicted)**	**LLN* (lower 2.5%)**	**ULN* (upper 2.5%)**	**z-score (provided only if an observed value is manually entered)***
	ENTER*		**Enter to see z-scores**				
ID	EMB0105	RR (brpm)	11.7	15.0	9.4	23.7	-1.04
Age (year)	40	Ti (sec)	1.33	1.62	1.08	2.66	-0.91
Height (cm)	180	Te (sec)	3.67	2.28	1.38	3.76	1.86
Sex (M:F)	M	Ti/Ttot (duty cycle)	0.27	0.42	0.35	0.48	-4.26
		Relative thoracic contribution (%)	53.0	50.9	27.9	73.8	0.18
		Breath Phase (degrees)	5.8	3.9	1.7	12.8	0.63
		IE50	2.74	1.29	0.96	1.88	3.56

*Valid range for Age is between 2 to 75, for Height is between 82 to 194cm and valid Sex entries are only M and F

*LLN and ULN correspond to *z*=-1.96 and *z*=1.96 respectivly

*Color code for z-scores:

- Green if z-score betewen -1.28 and 1.28
- Yellow: 1.28<abs(z)<1.64
- Orange: 1.64<abs(z)<1.96
- Red: abs(z)>1.96

Figure 1.A screen shot of the SLP normative value calculator. Entries for the observed column are arbitrary and only serve to demonstrate the layout of the normative value calculator.

Visual representation of the reference equations

The authors believe visual representation of the equations will be helpful to readers. Implementing this is not straightforward as the predictive equations depend on multiple variables (i.e. age and height). It is however possible to generate a predictive model for height based on age and then substitute the predicted values of height in the models that depend on both age and height, this way we can visualise the progression of each parameter with age in a simple two dimensional graph. The predictive model for height is depicted and explained below. We strongly emphasise that this is purely done for a presentation purpose. For accurate calculation of the normative values only use the SLP normative value calculator spreadsheet provided in the supplementary material.

Predictive model for height

Using the data in the current study a predictive model for height was developed using GAMLSS. A fifth order polynomial model was found to adequately describe the relationship between height and age. Figure 2 visualises this model.

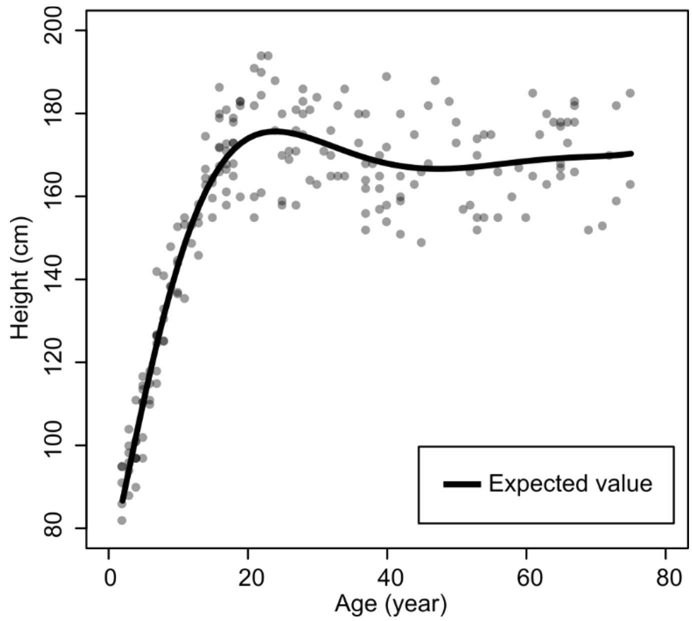


Figure 2. Predictive model of height using age. GAMLSS was used to develop this model. The model for mu took the following form $Height = a_0 + a_1 \times Age + a_2 \times Age^2 + a_3 \times Age^3 + a_4 \times Age^4 + a_5 \times Age^5$ where a_0=4.26, a_1=0.11, a_2=-0.005, a_3=0.0001, a_4=-1.07e-6 and a_5=4.09e-9. The distribution for the fit was Box-Cox Power exponential original (BCPEo), a 4-parameter distribution. Terms for sigma, nu and tau were constants and respectively equal to 0.058, 0.62 and 3.8.

Small-scale clinical validation of the developed reference equations

We tested the developed reference equations here in an independent mixed cohort including both healthy subjects (N=10) and patients (N=24) with varying respiratory disorders and severities. We defined a respiratory pattern as clinically abnormal if any of the seven parameters in the study was found to be statistically abnormal (i.e. for each subject, if at least one parameter fell outside the normal range, we classified that subject's respiratory pattern as abnormal). Using this straightforward criterion, we found 17/24 patients classified as abnormal (70.8% sensitive) and 10/10 subjects without a history of a respiratory disease as normal (100% specific). Sensitivity and specificity figures could be further improved by adopting a more sophisticated criterion for abnormality detection, but in the interest of clarity we retain the criterion above since its message is clear and simple, if a tidal breathing parameter is statistically abnormal, the respiratory pattern is likely to be clinically abnormal too, in other words, statistical abnormality translates directly into clinical abnormality. Further information about this clinical validation can be found in our recent abstract publication here [13]. This work is currently being expanded and written up for future publication.

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Please Insert Subject Details in the ENTER Column

The current reference ranges are based on 198 measurements on seated normal subjects (no history or respiratory disease).

Subject Info			SLP Parameter	Observed (measured)	Expected value (predicted)	LLN* (lower 2.5%)	ULN* (upper 2.5%)	z-score (provided only if there is an observed value manually entered)*
	ENTER*			Enter to see z-scores (optional)				
ID	SubjectX		RR (brpm)	11.7	15.0	9.4	23.7	-1.05
Age (year)	52		Ti (sec)	1.33	1.58	1.06	2.60	-0.80
Height (cm)	172		Te (sec)	3.67	2.39	1.45	3.95	1.67
Sex (M:F)	M		Ti/Ttot (duty cycle)	0.27	0.41	0.34	0.47	-3.96
			Relative thoracic contribution (%)	53.0	52.4	29.4	75.3	0.05
			Breath Phase (degrees)	5.8	3.5	1.6	9.8	0.98
			IE50	2.74	1.29	0.96	1.88	3.56

*Valid range for Age is between 2 to 75, for Height is between 82 to 194cm and valid Sex entries are only M and F

*LLN and ULN correspond to *z=-1.96* and *z=1.96* respectivly

*Color code for z-scores: Green if z-score betewen -1.28 and 1.28 | Yellow: *1.28<abs(z)<1.64* | Orange: *1.64<abs(z)<1.96* | Red: *abs(z)>1.96*

Please ensure entries for Age are in years and entries for Height are in cm.