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]

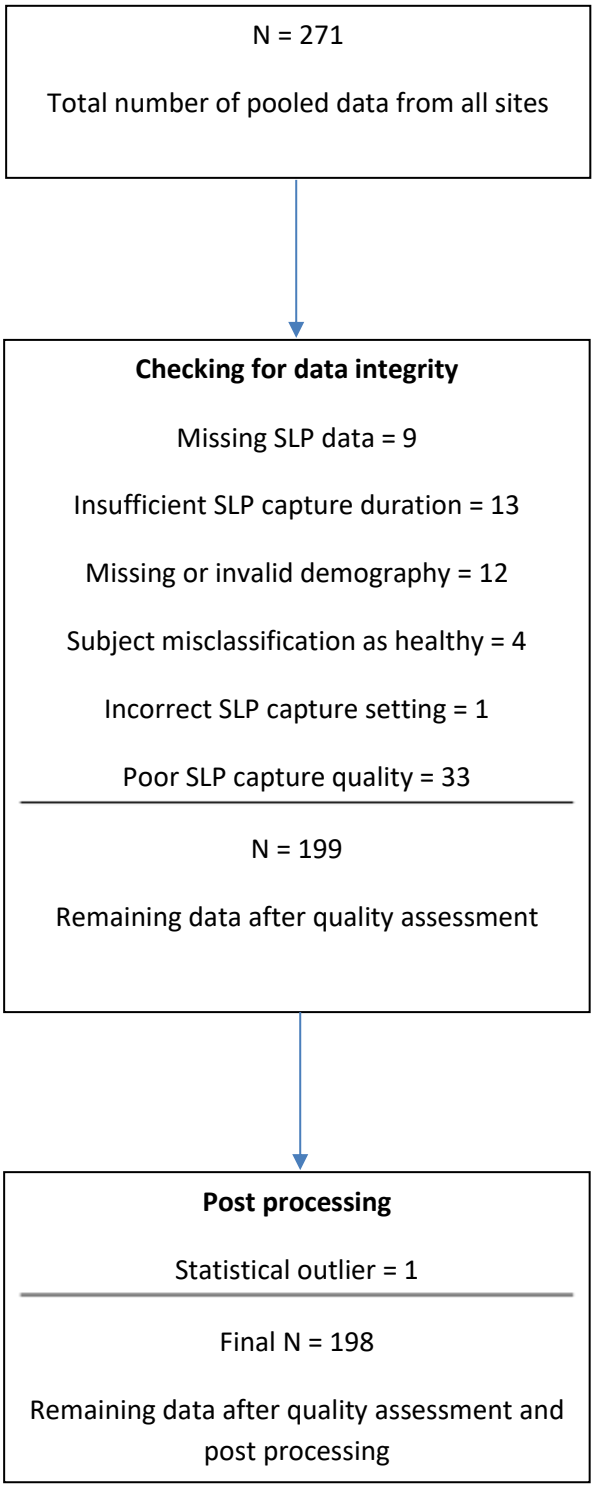
Data

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.

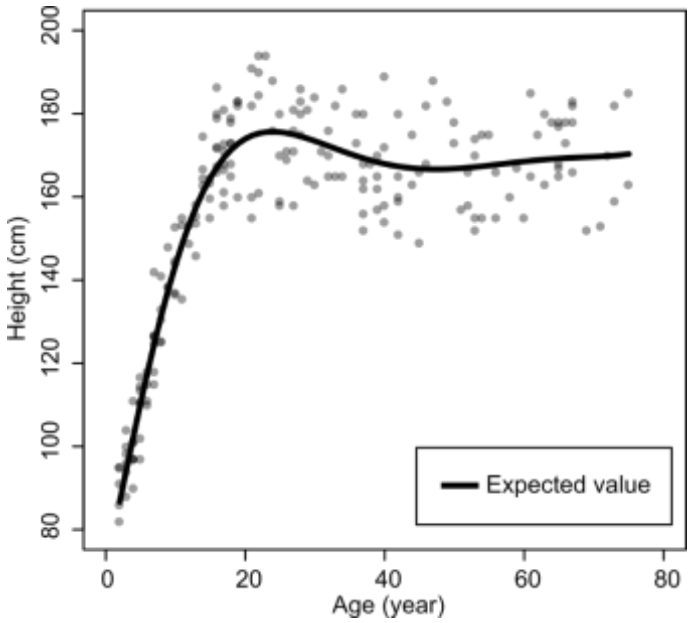


Figure 2. Predictive model of height using age. GAMLSS was used to develop this model. The model for mu took the following form $Height = a_0 + a_1 \times Age + a_2 \times Age^2 + a_3 \times Age^3 + a_4 \times Age^4 + a_5 \times Age^5$ where a_0=4.26, a_1=0.11, a_2=-0.005, a_3=0.0001, a_4=-1.07e-6 and 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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