Reference equations for tidal breathing parameters using structured light plethysmography

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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 (f_R), inspiratory time (t_I), expiratory time (t_E), duty cycle (t_I/total breath time), phase (thoraco-abdominal asynchrony (TAA)), relative thoracic contribution (RTC) and tidal inspiratory/expiratory flow at 50% volume (IE50).

Reference equations were developed based on a cohort of 198 seated healthy subjects (age 2–75 years, height 82–194 cm, 108 males). We adopted the same methodological approach as the Global Lung Function Initiative (GLI) report on spirometric reference equations. 5 min of tidal breathing was recorded per subject. Parameters were summarised with their medians. The supplementary material provided is an integral part of this work and a reference range calculator is provided therein.

We found predicted f_R to decrease with age and height rapidly in the first 20 years and slowly thereafter. Expected t_I, t_E and RTC followed the opposite trend. RTC was 6.7% higher in females. Duty cycle increased with age, peaked at 13 years and decreased thereafter. 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 that clinicians and researchers can identify tidal breathing patterns in disease and better understand and interpret SLP and tidal breathing data.

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A set of reference equations for seven key tidal breathing parameters measured using structured light plethysmography (SLP) to help clinicians better understand and interpret SLP data and the value of tidal breathing patterns https://bit.ly/2Og2H3h

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Introduction

While 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. In addition, there is evidence that respiratory viruses can be transmitted in aerosols generated by asymptomatic individuals [1], especially during the forced manoeuvres of lung function tests [2]. Measurement of tidal breathing patterns is easier to perform, provides a complementary method to traditional lung function and breathing assessment in children and adults [3, 4] and minimises cross-infection risk.

Structured light plethysmography (SLP) is an established technique for non-contact measurement of respiratory motion [5–11]. A checkerboard pattern of light is projected onto the subject's thoraco-abdominal 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 thoraco-abdominal wall can be spatially averaged over different regions (compartments; *e.g.* chest and/or abdomen) to generate one-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 using a spirometer [5].

The pattern of tidal breathing can be derived from the displacement of the thoraco-abdominal wall and a number of tidal breathing parameters can be calculated from this pattern. We report seven key tidal breathing parameters measured using SLP: respiratory rate (f_R), inspiratory time (t_I), expiratory time (t_E), duty cycle (t_I/t_{tot}), thoraco-abdominal asynchrony (TAA), relative thoracic contribution (RTC) and tidal inspiratory/expiratory flow at 50% of tidal volume (IE50; also a surrogate measure of airway obstruction [6]). The calculation of IE50 is not based on absolute flow and volume measurements; rather, it is derived from the movement of the thoraco-abdominal wall (analogous to volume) and the first derivative of thoraco-abdominal wall movement (analogous to flow).

We provide a set of growth-adjusted reference equations for these parameters. They were selected as they had shown clinical utility. Supplementary table 1 lists these parameters, their definitions and their clinical utility. These are the first reference data of this kind, and the authors anticipate that it will aid clinicians

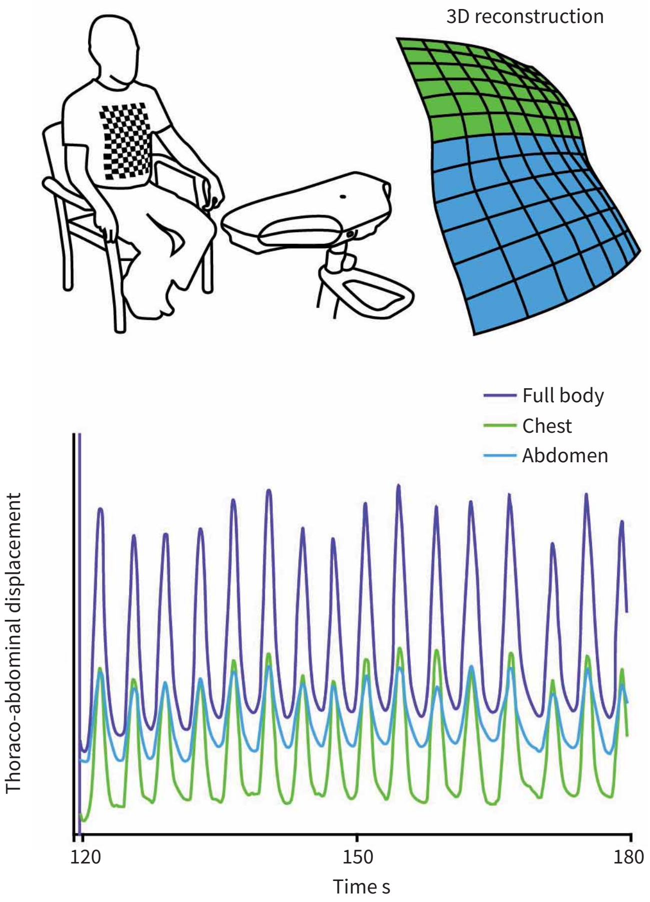

FIGURE 1 Working principle of structured light plethysmography. The green trace corresponds to the thoracic movement, the blue trace shows the abdominal movement and the purple trace is the summation of blue and green traces, reflecting the movement of the entire thoraco-abdominal wall.

and researchers to better quantify, understand and interpret SLP data and tidal breathing patterns. The supplementary material provided is an integral part of this study and it is highly recommended 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; Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; University Hospital North Midlands (UHNM), Stoke-on-Trent, UK) were collated retrospectively. Data collected from QE were control data for an α_1-antitrypsin deficiency study [12]. Data from Addenbrooke's Hospital 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 [6, 7]. 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 min of SLP capture in seated position and had a body mass index <40 $\text{kg}\cdot\text{m}^{-2}$. Subjects wore a taut white t-shirt (or the test was done on bare skin). In total, 73 datasets were excluded from the analysis, details of which can be found in the supplementary material (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 are detailed in the SLP signal processing section in the report by MOTAMEDI-FAKHR *et al.* [8]. Parameters were summarised for each 5-min epoch by taking the median. Each dataset was accompanied by subject age, sex, height and weight. Ethnicity was not specified. None of the subjects were sedated for measurement. Age of subjects ranged from 2 to 75 years, height between 82 and 194 cm and weight between 14 and 149 kg. Further information on data quality assessment, exclusions and demographic information can be found in the supplementary material (data section).

Statistical analyses

We adopted the same methodological approach as the Global Lung Function Initiative (GLI) publication on spirometric normative equations [13]. The Generalised Additive Models for Location, Scale and Shape (GAMLSS) 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 scatterplots of each parameter against age, height, weight and sex to identify the regressors. Distribution of the dependent variable (*e.g.* f_R, t_I, t_E) 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 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.

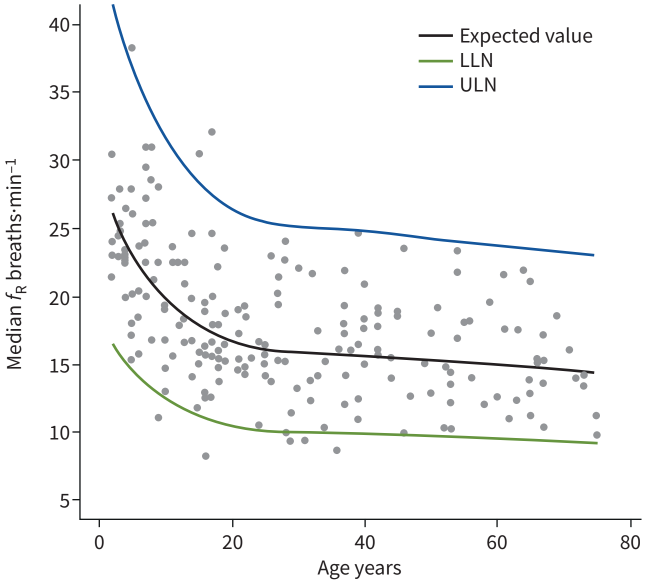

FIGURE 2 Growth-related changes in median respiratory rate (f_R). LLN: lower limit of normal; ULN: upper limit of normal.

The model for each parameter and its considerations are detailed in the supplementary material (equations section).

Results

An 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. In addition, it is possible to manually input observed values for each parameter and automatically obtain their corresponding z-scores. The calculator spreadsheet is available in the supplementary material. In the following section, the 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). The 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 f_R. Height entries are estimated rather than observed (see the visual representation of the reference equations section in the supplementary material for more information); the graph provides only an approximate guidance on the overall trend; for actual values use the normative value calculator spreadsheet.

Inspiratory time

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

Expiratory time

The model for t_E depends only on age; therefore, figure 4 accurately depicts the age-related changes in median t_E.

Duty cycle

t_I/t_{tot} increases during early life, peaks at age 13 years, and decreases gradually thereafter. t_I/t_{tot} is dependent on both age and height, and therefore figure 5 provides approximate guidance on the overall trend.

Relative thoracic contribution

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

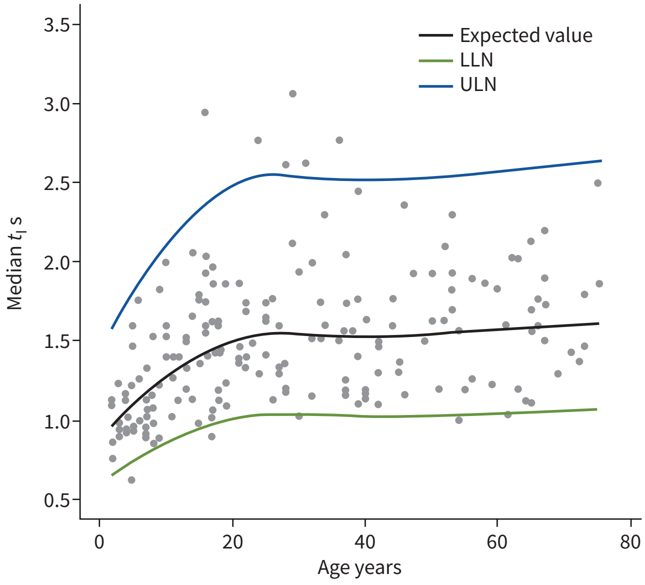

FIGURE 3 Growth-related change in median inspiratory time (t_I). LLN: lower limit of normal; ULN: upper limit of normal.

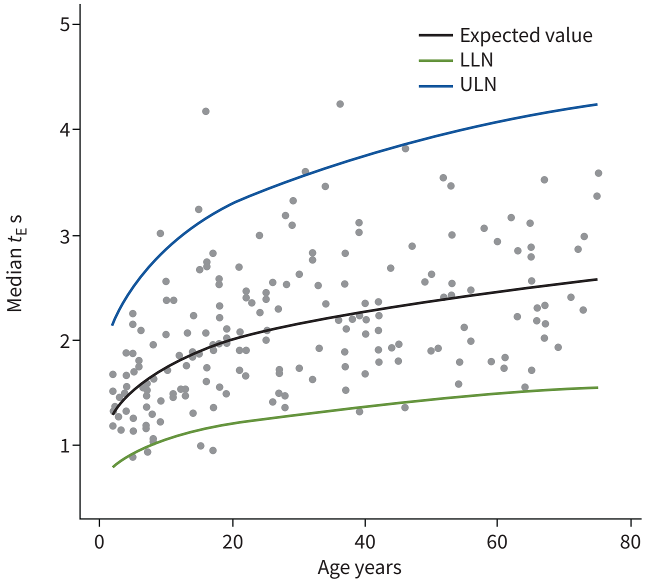

FIGURE 4 Growth-related change in median expiratory time (t_E). LLN: lower limit of normal; ULN: upper limit of normal.

Thoraco-abdominal asynchrony

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.

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 of this.

Discussion

This study provides, for the first time, a preliminary set of normative (reference) equations for seven tidal breathing parameters of respiratory rate (f_R), inspiratory time (t_I), expiratory time (t_E), duty cycle, thoraco-abdominal asynchrony (TAA), relative thoracic contribution (RTC) and IE50 measured using SLP. Here, we discuss our findings regarding each parameter in relation to the existing body of literature.

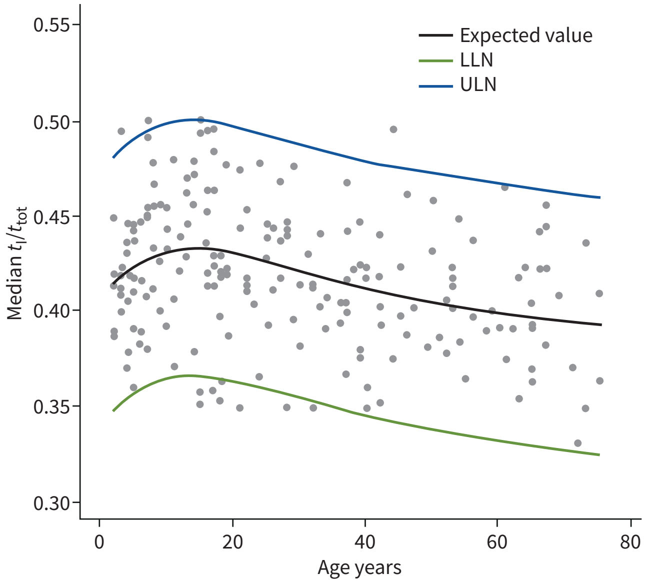

FIGURE 5 Growth-related change in median duty cycle (t_I/t_{tot}). LLN: lower limit of normal; ULN: upper limit of normal; t_I: inspiratory time; t_{tot}: total breath time.

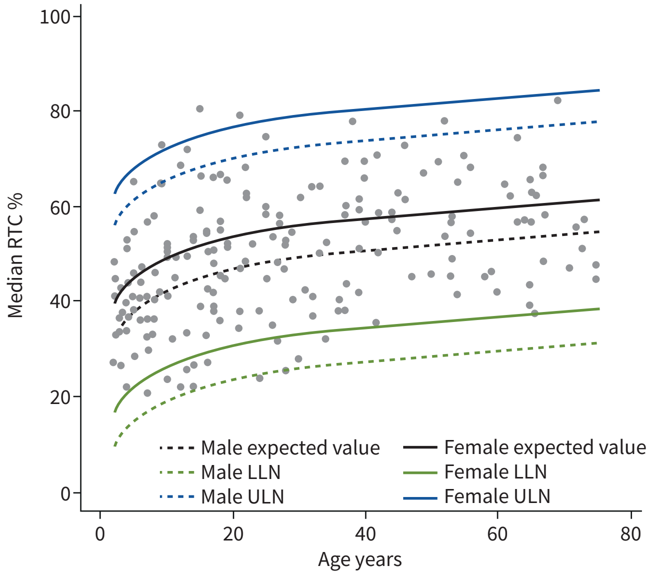

FIGURE 6 Growth-related change in median relative thoracic contribution (RTC) in males and females. LLN: lower limit of normal; ULN: upper limit of normal.

Respiratory rate

Normative equations or reference ranges for f_{R} have been covered in the literature for infants [17] and children aged $\leqslant$3 years by Gagliardi and Rusconi [18]. They used body weight as the sole predictor of respiratory rate in 635 infants and children weighing 14–20 kg. These data are similar, with f_{R} ranging from 18 to 35 breaths·min^{-1} (judging from the scatterplot in figure 2 therein) and between 18 and 32 breaths·min^{-1} in our study.

For children aged 4–16 years Wallis *et al.* [19] provide a set of normative equations based on direct measurement of f_{R} by observing the movement of the chest in 1109 healthy resting children in a seated position. The reported ULN and LLN (*i.e.* upper and lower 2.5%) are narrower than in our study.

Furthermore, our expected values and trend of changing f_{R} with age agrees with a review article providing reference equation for f_{R} in the first 18 years of life. Fleming *et al.* [20] reported a rapid reduction in f_{R} and its variability, most pronounced during early life, particularly in those aged 2–3 years.

In adults, the norm seems to be a constant 12–20 breaths·min^{-1} range for f_{R} [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 agreement.

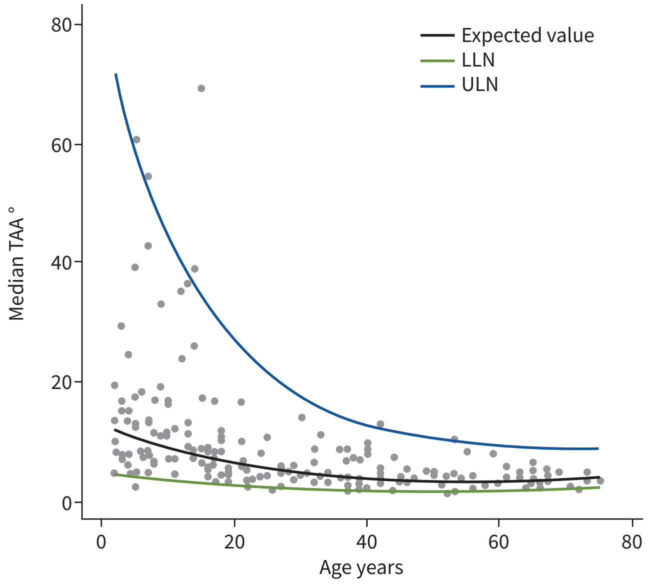

FIGURE 7 Growth-related change in median thoraco-abdominal asynchrony (TAA). LLN: lower limit of normal; ULN: upper limit of normal.

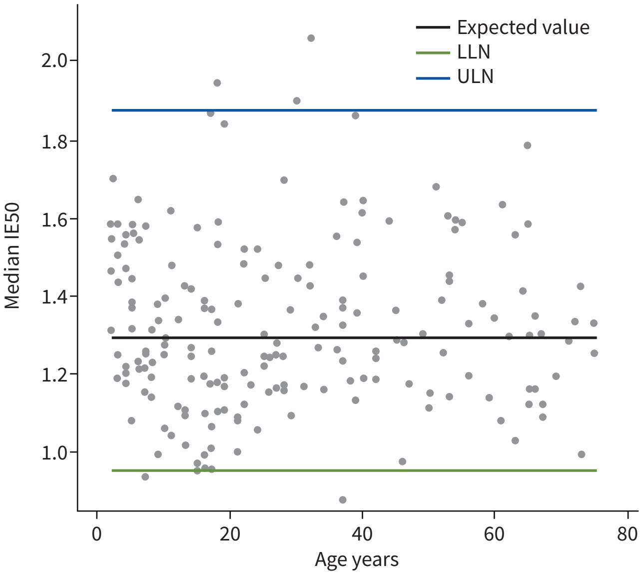

FIGURE 8 Tidal inspiratory/expiratory flow at 50% volume (IE50) does not correlate with age, height or sex. Expected value, LLN and ULN were 1.29, 0.96 and 1.88, respectively. LLN: lower limit of normal; ULN: upper limit of normal.

Inspiratory time, expiratory time and duty cycle

Normative values or reference equations are not well established for t_{I} and t_{E} during quiet tidal breathing. Most studies pertain to mechanical ventilation. However, indications of what might constitute a normal t_{I} and $t_{\mathrm{I}}/t_{\mathrm{tot}}$ do exist. Tobin *et al.* [22] reported a normal t_{I} of 1.6±0.3 s in young healthy subjects (aged 20–50 years, n=47) and 1.67±0.35 s in older healthy subjects (aged 60–81 years, n=18). Note that the reported values are mean±SD measured in the supine position. The average age for the young and old cohorts were 29 and 69 years, respectively. Using our equation to calculate t_{I} by substituting 29 years for age and the predicted height from our data (≈174 cm), the predicted value was 1.54 s. For a 69-year-old with an estimated height of ∼170 cm, the predicted t_{I} was 1.59 s. This is a crude comparison, and the discrepancies can be attributed to different measurement devices (SLP *versus* respiratory inductance plethysmography (RIP)), subject position (seated *versus* supine), summary statistic (median *versus* mean) and possibly to a different demographic. However, the trend and the difference between old and young cohorts is confirmed in our data. We found that t_{I} increases with age and height up to ∼20 years of life and more slowly thereafter.

t_{E} is similar to t_{I}. There are few published studies looking at normative t_{E} 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 t_{E} increases more rapidly during the first 20 years of life and gradually (linearly) thereafter.

Duty cycle ($t_{\mathrm{I}}/t_{\mathrm{tot}}$) 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. Parreira *et al.* [24] measured $t_{\mathrm{I}}/t_{\mathrm{tot}}$ 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 (aged 20–39 years), but not in the other age bands. In our equation for $t_{\mathrm{I}}/t_{\mathrm{tot}}$, sex has not been identified as a determining factor ($t_{\mathrm{I}}/t_{\mathrm{tot}}$ was predicted by age and height only). Using optoelectronic plethysmography (OEP) with 83 healthy adult subjects, Mendes *et al.* [25] reported that $t_{\mathrm{I}}/t_{\mathrm{tot}}$ did not change with posture or sex, which confirms our finding. Furthermore, actual values reported for expected $t_{\mathrm{I}}/t_{\mathrm{tot}}$ in healthy adults are broadly similar to ours, with Tobin *et al.* [22] and Parreira *et al.* [24] reporting an average $t_{\mathrm{I}}/t_{\mathrm{tot}}$ of approximately 0.42±0.03 and 0.39±0.04, respectively. Wilkens *et al.* [26] reported an average duty cycle of 0.37 in 10 healthy adults at rest using OEP. This appears to be lower than our estimated expected value for similar age and height, although this difference might be explained by the small sample size (10 *versus* 198) and use of an alternative summary statsitic (mean *versus* median). There are no published normative values of $t_{\mathrm{I}}/t_{\mathrm{tot}}$ for children, and therefore our study provides these unique data.

Thoraco-abdominal asynchrony

Phase-angle or thoraco-abdominal asynchrony has been used to assess respiratory function in children [6, 7, 27] and adults [8, 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° in a cohort of 50 young children (aged 3–5 years) 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° *versus* 13°). This is probably due to the difference in position of subjects (supine *versus* seated). A higher TAA in the supine position compared to seated is shown in MAYER *et al.* [29]. TAA in healthy subjects in a seated position is reported elsewhere [28, 30]. The number of healthy subjects is low (n=10 and n=9 at rest, respectively), and the method for calculation of phase differs slightly from what has been used herein. 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 (low TAA in adult subjects, generally ~5° and not exceeding 10°).

Relative thoracic contribution

RTC 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 [9], 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 ~6.7% higher in females than in males across all ages included in the study. Our results partially fit with the account of ribcage contribution when it comes to females having a higher ribcage contribution [25], but differs in the reported trend of decreasing ribcage contribution with age in adult subjects, seen in that and other studies [25, 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 pronounced 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 discrepancy 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 the aforementioned 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; as such, published normative values or reference equations for IE50 are currently unknown. As a surrogate measure of airway obstruction [6] it quantifies the effective shape of tidal breathing flow/volume 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 are yet to be collected. Interest in SLP is growing, and new data will augment the datasets 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 confirms this and shows promise [40]. More information on the validation study can also be found in the final section of the supplementary material. 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 were 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 SLP. Expected normative values for f_R, t_I, t_I/t_{tot} and TAA agree well with previous studies.

RTC in females was higher than in males, which is in line with the existing literature. However, the increasing trend of adult RTC with age in our study 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 as a whole remain inconsistent in the literature.

We have unique normative values for t_E 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 supplementary material which should help clinicians and researchers better interpret SLP data and tidal breathing in general. This may be of particular benefit given the coronavirus disease 2019 pandemic, since tidal breathing may be an alternative, non-aerosol-generating procedure for lung function assessment.

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Conflict of interest: S. Motamedi-Fakhr is a full-time employee of PneumaCare Limited. R. Iles is a past employee, founder and shareholder of PneumaCare. N. Barker has nothing to disclose. J. Alexander has nothing to disclose. B.G. Cooper reports that his department has had the free loan of Thora 3 Di device from Pneumacare for the past 5 years as it has developed clinical use of the device.

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