

**SERIES "STANDARDS FOR INFANT RESPIRATORY FUNCTION TESTING: ERSIATS
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**Plethysmographic measurements of lung volume
and airway resistance**

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Task Force on Standards for Infant Respiratory Function Testing

Plethysmographic measurements of lung volume and airway resistance. J. Stocks, S. Godfrey, C. Beardsmore, E. Bar-Yishay, R. Castile, on behalf of the ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. ©ERS Journals Ltd 2001.

ABSTRACT: Functional residual capacity (FRC) is the only static lung volume that can be measured routinely in infants. It is important for interpreting volume-dependent pulmonary mechanics such as airway resistance or forced expiratory flows, and for defining normal lung growth. Despite requiring complex equipment, the plethysmographic method for measuring FRC is very simple to apply and, unlike the gas dilution techniques, enables repeat measures of lung volume to be obtained within a few minutes. This method has the further advantage that with suitable adaptations to the equipment, simultaneous measurements of airway resistance can also be obtained.

The aim of this paper is to provide recommendations pertaining to equipment requirements, study procedures and reporting of data for plethysmographic measurements in infants. Implementation of these recommendations should help to ensure that such measurements are as accurate as possible and that meaningful comparisons can be made between data collected in different centres or with different equipment. These guidelines cover numerous aspects including terminology and definitions, equipment, data acquisition and analysis and reporting of results and also highlight areas where further research is needed before consensus can be reached.

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The present paper represents one of a series that have been produced by the European Respiratory Society/American Thoracic Society Task Force on Standards for Infant Respiratory Function Tests. The aim of this paper is to summarize what is currently seen to be good laboratory practice, and to provide recommendations

for both users and manufacturers of infant lung function equipment and software with respect to plethysmographic measurements of lung volume and airway resistance in infants. These recommendations have been developed after widespread communication on an international level and are directed towards future

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developments in this field, including the use of more automated and standardized equipment than has been used in many clinical and research centres in the past.

The recommendations presented here do not invalidate previously published data collected with less automated systems but provide guidance for current and future applications. It is recognized that this paper will need regular updating in response to advances in technology and understanding. In the meantime, every attempt has been made to avoid being too prescriptive to allow for future developments, while offering guidance on minimum standards for those developing equipment and performing the tests.

Recommendations regarding measurement of airway resistance have been restricted to those obtained under BTPS (Body temperature and pressure, saturated) conditions, using a heated rebreathing bag. This is the only approach that has been thoroughly assessed in infants and with the exception of the earliest trials in the 1960s, all published results of airway resistance in infants have been obtained using this approach. New methods such as those utilizing electronic/mathematical algorithms to compensate for thermal artefacts [1, 2] may eventually prove to be advantageous, and will certainly be simpler to operate. These will, however, need to be compared with the "gold standard" BTPS method before being adopted for routine use.

The theoretical background and practical details of how to apply this technique and interpret results have been described previously in a book published by the task force, which collates much of the relevant information and discusses background issues that may influence measurements [3]. Further details regarding equipment and software specifications are described elsewhere [4, 5]. It is anticipated that acceptance and application of these recommendations will be of particular value when attempting to compare data between centres, develop or use reference data, or participate in multicentre trials which use parameters of infant plethysmography as outcome measures.

Terminology and definitions

The infant whole body plethysmograph is a valuable tool for obtaining simultaneous measurements of lung volume and airways resistance [3]. This technique aims to measure functional residual capacity (FRC_p or FRC_{pleth}) and airway resistance (R_{aw}). From these, other key parameters such as airway conductance (G_{aw} = the reciprocal of R_{aw}), specific resistance (sR_{aw} = resistance \times FRC), and specific conductance (sG_{aw} = G_{aw} /FRC) can be calculated. In practice, the baby lies inside the plethysmograph, a rigid, closed container, and breathes through a pneumotachometer (PNT), which records changes in tidal flow and volume. While the infant is breathing quietly, the airway opening is occluded briefly using a remotely controlled shutter. The infant makes respiratory efforts against this obstruction, thereby compressing and rarefying the thoracic gas. It is assumed that during periods of no airflow, pressure at the airway opening reflects changes in alveolar pressure. By relating these changes to changes in alveolar volume, which are

reflected by changes in the plethysmographic signal, the total volume of gas within the thorax at the moment of occlusion can be calculated. Similarly, providing the respired gas can be kept at BTPS conditions, changes in plethysmographic pressure during spontaneous breathing are inversely proportional to changes in alveolar pressure. By relating changes in box (alveolar) pressure to simultaneous changes in flow at the airway opening, airway resistance (R_{aw}) can be calculated.

The term "airway" resistance should be reserved for techniques such as plethysmography, which relate changes in alveolar pressure to airflow. It should not be used to describe pulmonary (lung tissue plus airway) resistance as calculated from changes in transpulmonary (oesophageal) pressure, or respiratory (airway plus tissue plus chest wall) resistance as measured from changes in pressure at the airway opening. Other documents in this series describe alternative methods of assessing FRC [6] and resistance [7]. A full list of definitions, recommended abbreviations and units are included in the Appendix.

Equipment

Further details and justification of the recommendations presented have been published in previous documents in this series [4, 5, 8, 9].

Plethysmograph

Recommendations when using the plethysmograph:

- 1) The dimensions of the plethysmographic chamber should generally be sufficient to accommodate infants up to ~ 15 kg or 85 cm length. For such infants, a box of ~ 70 – 100 L is usually adequate. Centres wishing to assess preschool children may require a somewhat larger box, whereas those assessing preterm or newborn infants may require a smaller chamber to achieve adequate resolution.
- 2) Particular attention is required to ensure sufficient room for manipulation of the mask and breathing apparatus when the infant is *in situ*, whilst maintaining a streamlined design to facilitate rapid and complete pressure equilibration within the chamber.
- 3) Clear vision and rapid access (< 2 s) to the child is essential at all times.
- 4) The compensation chamber should have identical thermal and mechanical characteristics as the plethysmographic chamber, although a smaller capacity (25–50%) is usually satisfactory.
- 5) The box should be constructed of suitable materials to ensure adequate heat exchange and should not be excessively insulated. Net loss through the walls should equal net gain from infant and equipment to ensure rapid thermal equilibration.
- 6) The use of air conditioning and/or fans within the box should be avoided except for the use of a small isolated fan within the rebreathing bag during R_{aw} measurement.
- 7) Compressible objects within the box (e.g. avoid foam mattresses) should be minimized.
- 8) Frequency response (amplitude and phase) should be satisfactory to 10 Hz [4, 5].
- 9) The combined time constant should be ~ 10 – 14 s (63% decay) or a half life of 6–9 s [9].
- 10) There should be a linear response of

the box signal to known inputs over a range of appropriate breathing frequencies (e.g. 20–100 breaths per minute (bpm)). If this is not achieved the box calibration factor will need to be adjusted according to the infant's precise respiratory pattern, which may vary considerably throughout the testing period [3]. 11) It is essential to check the linearity of the plethysmographic output over a suitable range of inputs. This should take into account the fact that changes in plethysmographic volume or pressure may be as small as 1–2 mL or Pa respectively during FRC measurements and even smaller during airway resistance measurement, especially in healthy infants. Such assessments will generally require specialized equipment [9]. 12) A standard lung model should be used to check the accuracy with which FRC can be measured. Ideally this should cover a range of volumes 30–500 mL, at frequencies 20–100 bpm. A narrower range of volumes and frequencies may be applicable according to the age range and clinical status of infants studied within a particular laboratory [4, 9]. Ideally such validation should be performed prior to release of any commercially available equipment. 13) Clear specifications must be provided by the manufacturers regarding the range of lung volumes that can be reliably measured by the system, particularly with respect to the lower range, since standard infant plethysmographs may not be suitable for assessing lung volumes in neonates or preterm infants.

Breathing apparatus

Recommendations for the breathing apparatus: 1) The PNT must be linear over the range of flows encountered, bearing in mind that relatively high flows may be recorded if there is any stimulation of breathing while the infant is switched into the heated rebreathing bag during assessments of R_{aw} . The PNT must remain linear when heated [4]. 2) The combined dead space of the PNT and occlusion shutter should ideally be $<2 \text{ mL}\cdot\text{kg}^{-1}$ together with the smallest possible mask to minimize dead space. This means that at least two sets of breathing apparatus will probably be required according to infant size to attain minimum dead space and maximum resolution. Spare sets should be available in case there are technical problems due to shutter failure, leaking connections and so forth. 3) The resistance of the combined apparatus should be $<20\%$ of the infant's intrinsic resistance at the highest flow likely to be encountered, *i.e.* in term neonates, $<0.7 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$ at $166 \text{ mL}\cdot\text{s}^{-1}$, whereas for a 1-yr-old, it should not exceed $0.5 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$ at $500 \text{ mL}\cdot\text{s}^{-1}$. 4) A low dead space, low resistive shutter is required. This shutter should not influence the linearity of PNT adversely. If lung volumes alone are being measured this can be a simple occlusion device. For airway resistance measurements, a two-valve system is required (see later), designed to optimize dead space, linearity and resistance. 5) Automated and remote control of the shutter is essential, as is the need for default to the open position in the event of any equipment or software failure. 6) Automated closure should be feasible at end inspiration (EI), end

expiration (EE), or other points through the breath as specified by the user. 7) Speed of valve opening and closing (excluding any lag time) should be $<75 \text{ ms}$. Most modern valves suitable for plethysmography close considerably faster than this. 8) At least two complete respiratory efforts against the occlusion are generally required for satisfactory assessments of FRC_p . It may therefore, be necessary to hold the occlusion for at least 10 s, although a default set to 8 s is generally satisfactory. 9) An alarm should sound if the occlusion exceeds 15 s or that designated by the user. 10) The shutter must be able to withstand pressures of $\pm 3 \text{ kPa}$ without any leaks or compressive effects. 11) A "shutter test" should be incorporated within the software and calibration protocol, so that the shutter can be checked prior to each study occasion. 12) The shutter must be easy to clean and reassemble. It should be light, with a suitable means of support and easy manipulation within the box. 13) Activation of the shutter should result in minimal volume change within the box and be as quiet as possible to avoid disturbing the infant or altering sleep state.

Mask

Factors to consider for successful employment of the mask: 1) Dead space of the mask should be measured by water displacement and 50% of this value subtracted to take into account the space occupied by the infant's face and the putty seal [4, 10]. 2) A very firm mask is essential to prevent errors due to compressive changes during occlusions when pressure swings of $\pm 1-2 \text{ kPa}$ may occur. 3) The use of therapeutic putty to achieve a good, airtight seal is recommended.

Additional equipment for airway resistance measurements under BTPS conditions

Additional equipment that is required for airway resistance measurements: 1) The apparatus will require two ports through which the infant can breathe. The first opens to the box, and the second connects to a heated rebreathing bag (HRB). Both ports should be controlled by remotely operating shutters so that the infant can be switched to breathe through the desired port. 2) Both the apparatus and the HRB should incorporate servo-controlled heating elements. 3) The HRB should be completely contained within the box, be of approximately 1 L capacity, and be made of highly compliant but nonelastic material. It is essential that no pressure changes occur within the bag itself while the infant is rebreathing. 4) An easily accessible port through which the HRB can be emptied (a vacuum source) and refilled with heated humidified air/ O_2 is required. Adequate humidification is essential for accurate measurements. 5) A small fan to circulate the air within the bag has been found to improve temperature control.

Transducers

Ideal transducer parameters include (see also previous publications on equipment specifications [4]): 1)

A requirement for 3 perfectly matched transducers. 2) The range of signals encountered to cover: box pressure: range ± 0.1 kPa (*i.e.* 1 cmH₂O); airway opening pressure ± 2 kPa (20 cmH₂O) (± 5 kPa transducer will suffice); flow: during R_{aw} measurements, peak flows vary according to infant age and weight from < 100 mL·s⁻¹ in neonates to as high as 400 mL·s⁻¹ at around 1 yr [11]. Care should be taken to avoid excessive rebreathing (and increased end-tidal partial pressure of carbon dioxide (P_{et,CO_2})) which may result in significantly elevated flows. 3) Any transducer tubing should be noncompliant (stiff), perfectly matched on both sides of the transducers and of minimal length. Many modern systems now use solid state transducers. 4) All transducers should be checked for similar frequency response to at least 10 Hz while set up as for use during lung function tests, with all connections *in situ* [9].

Data acquisition and signal processing

Data acquisition requirements are dealt with elsewhere in this series [5]. Points of particular relevance to plethysmographic measurements are discussed in the present paper.

Recommended sampling rate

The recommended sampling rate is 200 Hz since this will be adequate for measurements of both R_{aw} and FRC_p . If only lung volumes are being measured, a lower sampling rate of 100 Hz would generally suffice.

BTPS conditions

During adult plethysmography, temperature measurements close to the PNT screen have indicated that considerable warming of inspired air may occur by the time inspired air reaches the subject (J. Reinstaedtler, Erich Jaeger GmbH, Hochberg, Germany, personal communication). By contrast, considerable deconditioning of the gas may occur during expiration such that some adaptation to the conventional BTPS correction may be advisable. Since equivalent data are not available in infants, it is currently recommended that the conventional approach whereby inspiratory air is corrected to BTPS whereas expired gas is assumed to be at BTPS be adopted. This approach may however, result in an upward drift of tidal volume if inspiratory volumes are consistently over corrected and expiratory volumes under corrected with respect to true conditions at the PNT at the moment of measurement. It is therefore, suggested that the magnitude of tidal volume drift is routinely recorded to assist in further investigation of this problem. Recommendations are as follows: 1) For calculation of FRC_p : when occlusions are performed above the end expiratory level (EEL), the volume inspired above the EEL must be converted to BTPS conditions prior to subtraction from the total occluded gas volume (TOGV) [8]. Since plethysmographic FRC

is measured under BTPS conditions, additional correction of the measured lung volumes is not required. 2) During airway resistance measurements: in systems where there is automatic BTPS correction of tidal breathing data, with intermittent use of a heated rebreathing bag for R_{aw} measurements, care must be taken to ensure that flows and volumes collected under BTPS conditions are not further corrected! 3) Ambient temperature: the temperature used for BTPS corrections should ideally be that within the box, but room temperature on the day of study will suffice since this is generally within a few degrees of that of the box with the baby *in situ*. 4) Ambient relative humidity: ideally, the value measured in the laboratory on the day of study should be used in BTPS corrections. If this is not available, an approximation of 50% humidity is generally substituted. 5) Barometric pressure: the barometric pressure should be obtained from a room barometer or the local meteorological office on the day of study. 6) Gas mixtures other than air: options should be available within the software to enter the gas mixture used on the day of study if this is other than air. Thus if infants are receiving supplemental oxygen, an automated correction for differences in density and viscosity should be applied by the software [8].

Drift correction of box signal

The box volume signal tends to drift during tidal breathing, due to slight increases in temperature, and in the opposite direction during the occlusion, when transfer of thermal energy into the box from respiration ceases. It is important to ensure that thermal equilibrium has occurred, with minimal drift, prior to performing the occlusion. It is important to observe the magnitude of this drift during the monitoring and data collection period to assess when equilibration has occurred. However, drift correction of the box signal prior to displaying recorded signals is essential to assess the phase relationships between the box signal and either flow (R_{aw}) or airway opening pressure (FRC_p). Various algorithms have been proposed, as discussed later.

Identification of end expiratory level

There are a number of factors to consider when identifying the EEL: 1) It is vital to establish a representative baseline EEL for accurate estimations of FRC_p irrespective of whether EE or EI occlusions are performed. The calculated EEL must be displayed clearly on the time-based trace so that the operator can evaluate whether a representative level has been selected. 2) The tidal volume signal must be stable to estimate EEL accurately. The various factors that may contribute to a drift of the tidal volume signal and the way in which this can be corrected have been discussed in detail elsewhere [8]. The drift correction algorithm uses the EE points from each epoch of breathing to assess the drift. The more breaths that are available, the more accurate this correction is likely to be. It is also important to apply this drift correction to the

postocclusion tidal volume data. 3) It is important to check for any shift in EEL postocclusion. This can indicate a leak around the mask [12]. 4) The facility to rezero flow to correct for any flow offset should be available during both data collection and analysis.

Calibration

To ensure adequate equipment calibration (see previous documents in this series for additional details regarding equipment calibration [4, 8]): 1) All channels should be calibrated, or a calibration check performed, prior to every infant study according to the manufacturer's recommendations. 2) It is vital that calibration tools are checked regularly. 3) Ideally, calibration of the plethysmograph should be performed using an automated sinusoidal pump with a variable frequency and volume. The use of automated calibration procedures is recommended, but must be intermittently checked manually. 4) Calibration must be performed under identical conditions as during measurements, for example with the PNT attached to the shutter block. 5) If the inspired gas differs from room air, *e.g.* during measurements of R_{aw} , deviations in gas viscosity must be taken into account [8]. 6) Calibration factors/checks should be displayed, recorded and saved with infant details on each occasion for subsequent quality control checks.

Monitor display

Modern software generally allows several displays simultaneously, thereby, greatly facilitating the monitoring of breathing patterns and quality control during data collection and analysis. The following displays are recommended during plethysmographic measurements: 1) For monitoring the infant: continuous display of tidal volume or flow and pressure at the airway opening (P_{ao}) whenever the mask and apparatus are connected, not just during data collection. 2) For lung volume measurements: time based displays of flow, volume, P_{ao} and V_{pleth} before, during and after the occlusion; X-Y plots of P_{ao} versus V_{pleth} during airway occlusions for FRC_p ; tabulation and/or cumulative plot of all relevant manoeuvres, to inform the operator how many acceptable measures of FRC_p have been obtained. 3) For resistance measurements: real time displays of flow, volume, P_{ao} and V_{pleth} both while breathing room air from the box and while rebreathing from the heated rebreathing bag; simultaneous X-Y plots of flow versus V_{pleth} ; tabulation and/or cumulative plot of all relevant manoeuvres, to inform the operator how many acceptable measures of R_{aw} have been obtained; composite flow versus V_{pleth} plot; composite R_{aw} - V_T plot.

Procedure

Measurement conditions

The measurement conditions have been previously discussed [13, 14]. Ideally, 2–3 min of baseline tidal volume recordings should precede the measurements of

R_{aw} and FRC to monitor breathing pattern and provide a broad assessment of sleep state. These can be obtained while the box is equilibrating. If a rebreathing bag is being used measurements of lung volume should precede those of airway resistance, unless care is taken to minimize the period of rebreathing. The baseline measures of FRC_p should also be made with minimal dead space and with no additional equipment such as "squeeze" jackets *in situ* [15]. Posture measurements should be performed in the supine position with the head in the midline and the neck slightly extended. Any deviations from this posture should be documented. Measurements should be restricted to periods when the infant is well settled, breathing regularly, with no eye or body movements.

Data collection

Points to consider for data collection (for further details see previous publications [3]) when measuring FRC_p include: checking for facemask leaks [3, 12]; leaving the box to equilibrate for 2–3 min after closing, or until the box signal has begun to stabilize with minimal drift; once the infant is breathing regularly with a well-established EEL, occlude at EI; holding occlusion for at least two complete respiratory efforts to allow for accurate drift correction; releasing occlusion and checking postocclusion EEL; checking phase relationship of P_{ao} versus V_{pleth} ; repeating until up to 5 (minimum 3) technically satisfactory EI occlusions have been obtained; and if desired, repeating at EE.

When making airway resistance measurements: fill the heated rebreathing bag (HRB) with moist warm air/ O_2 from the humidifier and allow it to reach BTPS conditions before switching the infant to breathe this mixture; during this period of adaptation, the box pressure is likely to drift and the box should therefore, remain vented or be vented frequently; the optimal temperature of gas in the HRB will depend somewhat on circuitry. The bag and apparatus need precise servo-control; adequate humidification is essential as are stringent safety measures to ensure that the infant is never exposed to inspired gases above 40°C; ensure that the bag does not touch the sides of the plethysmograph once the lid is closed and is not over-inflated; when the box signal is stable and the infant is breathing regularly switch the infant into the HRB at EE for no longer than 30 s to avoid excess buildup of CO_2 ; once stable pressure/flow loops are observed, switch the infant back to breathing air from the box; flush the bag thoroughly and repeat until at least three technically satisfactory epochs are obtained; CO_2 and O_2 concentrations in the HRB should be measured intermittently.

Data analysis

Calculation of lung volume

TOGV is determined from the ratio of $\Delta V_{pleth} : P_{ao}$ during respiratory efforts against the closed shutter. The tidal volume should be converted to BTPS conditions and any drift correction applied. To

calculate EEL prior to occlusion, the mean of at least 6 EE points after drift correction should be taken. The occluded volume above the EEL (V_{occ}) at BTPS conditions for subsequent subtraction from TOGV should be calculated. Some disturbance of the box signal inevitably occurs immediately after shutter closure. This is exacerbated by the fact that an expiratory pause usually occurs following EI occlusion. Since there is minimal true change in the V_{pleth} signal during this period, it is recommended that this portion of the trace should be excluded from the analysis. Evaluation of both the V_{pleth} drift and the V_{pleth}/P_{ao} relationship should therefore, not commence until the onset of the first inspiratory effort following EI occlusion or the second inspiratory tug if an EEO has been performed.

The box signal generally drifts during airway occlusions [3]. Drift correction is performed by identifying V_{pleth} at the transition points where the $P_{ao}=0$, where by definition V_{pleth} should also be zero. The change in V_{pleth} as a function of time between these points is then subtracted from the recorded value using a linear drift correction in time. As the baby only performs short efforts against the occluded shutter while relaxing in between, it is desirable to evaluate the signals only during the rapid changes in P_{ao} in order to improve the signal:noise ratio. To do this the signal trace is separated into single respiratory efforts, each consisting of a paired inspiratory (decreasing P_{ao}) and "expiratory" effort (increasing P_{ao}) against the occlusion. The slopes should be calculated by regression of V_{pleth} versus P_{ao} through all the data points that lie between the 5% limits, thereby truncating the peaks and troughs where noise is greatest. The 5% limit is calculated from the peak-to-trough P_{ao} per slope rather than the absolute maximum or minimum value during the whole occlusion. These limits should be user adjustable and be recorded with the results. Each inspiratory and the subsequent expiratory slope are combined to form a single "respiratory effort" slope by calculating the average angle of the two. The TOGV for each respiratory effort is calculated from the averaged slopes. It should be noted that some previous studies have been performed using calculations based on the inspiratory limb only. This practice is now discouraged.

Each individual effort should be displayed with the facility to exclude, if necessary, due to noise such as glottic closure. The mean value of the selected slopes within each occlusion are averaged to give a single result for that trial:

$$\text{TOGV} = \text{AS} \left(\frac{\Delta V_{pleth}}{\Delta P_{ao}} \right) \times (P_{amb} - P_{H_2O}) \times \left(\frac{V_{pleth} - V_{infant}}{V_{pleth}} \right) \quad (1)$$

where AS is the average slope, P_{amb} is the ambient (barometric) pressure, P_{H_2O} is the water vapour pressure at 37°C i.e. 6.25 kPa and V_{infant} is the infant's volume (L) which is equal to the infant's weight in kg. If the box has been calibrated without substituting the infant's weight by an equivalent volume of saline bags

the ratio of $\Delta V_{pleth}/\Delta P_{ao}$ must be corrected as shown. It must be noted that this method of calculation ensures that TOGV and hence FRC_p are calculated as the mean of both the inspired and expired efforts. Subtract V_{occ} from TOGV, together with the apparatus dead space ($V_{DS,app}$)

$$\text{FRC}_p = \text{TOGV} - V_{DS,app} - V_{occ} \quad (2)$$

where: $V_{DS,app}$ is the apparatus dead space (everything proximal to the shutter including any transducer tubing and mask) and V_{occ} is the volume occluded above EEL.

Criteria for technically satisfactory data have been described elsewhere [3, 16] but include the fact that: there should be no airflow during the occlusion, as shown by a zero flow signal (no flutter) and a stable EE baseline for tidal volume before and after the occlusion; and during the airway occlusion, changes in ΔP_{ao} and ΔV_{pleth} should be inphase, without evidence of glottic closure or leak.

Calculation of airways resistance

A full description of the derivation of equations for calculating sR_{aw} and R_{aw} has been published previously [3]. The essential quality criteria for assessment of plethysmographic R_{aw} is that there is a good phase relationship between the box signal and flow. Points to remember include: 1) Drift correction of the box signal during resistance measurements: prior to any calculations, V_{pleth} , must be drift corrected. This has to be performed on a breath-by-breath basis since changes in atmospheric pressure may influence the magnitude and direction of box signal drift, despite the presence of a compensatory chamber. Drift correction is performed by identifying the data sample points of V_{pleth} at the beginning of inspiration and end of the subsequent expiration, when alveolar pressure should be zero, and then subtracting the change over time from the box signal, by using a linear drift correction in time. The start and end of each breath is identified from simultaneous zero crossings on the flow trace; breaths should not be used for analysis if the drift is excessive. Signal to noise ratio may be considerably worse in healthy infants with low resistance and hence small changes in the plethysmographic signal. 2) Apparatus resistance (R_{app}): R_{app} should be calculated continuously and on a breath-by-breath basis by relating $\Delta P_{ao} : \Delta \text{flow}$ so that this can subsequently be subtracted from total measured resistance. 3) Calculation of specific airway resistance (R_{app}): providing there are no artefacts due to changes in the humidity and temperature of the respired gas, specific airway resistance can be calculated directly from the relationship of $\Delta V_{pleth}/\Delta \text{flow}$ prior to airway occlusion [1, 17–20] using the following equation:

$$sR_{aw} = \left(\frac{\Delta V_{pleth}}{\Delta \text{flow}} \right) \times (P_{amb} - P_{H_2O}) \times \left(\frac{V_{pleth} - V_{infant}}{V_{pleth}^*} \right) - sR_{app} \quad (3)$$

*This term can be omitted if the infant's weight was substituted during calibration of V_{pleth} . sR_{app} is

the specific resistance of the apparatus. This is calculated from the resistance of the apparatus at the specified flow and the lung volume of the baby *i.e.* $sR_{app} = R_{app} \times FRC_p$. If FRC_p is not available, a predicted value of $25 \text{ mL} \cdot \text{kg}^{-1}$ can be substituted; it should be noted that sR_{aw} can be calculated directly without the need to perform airway occlusions. However, a suitable correction for lung volume must be applied unless calculations are restricted to the V_{pleth}/flow relationship at low lung volumes close to FRC_{pleth} [21]. 4) Derivation of airways resistance: if technically acceptable measurements of FRC_p have been obtained, values of airway resistance (R_{aw}), airway conductance (G_{aw}) and specific airway conductance (sG_{aw}) can be subsequently derived, whereby:

$$R_{aw} = \frac{sR_{aw}}{FRC_{R_{aw}}} \quad (4)$$

where $FRC_{R_{aw}}$ is the lung volume at which R_{aw} is being calculated; $G_{aw} = 1/R_{aw}$ and $sG_{aw} = 1/sR_{aw}$. It must be noted that if deriving sG_{aw} simply by taking the reciprocal of mean sR_{aw} as described, the values obtained will differ slightly from those obtained if sG_{aw} was calculated separately on a breath-by-breath basis (harmonic *versus* arithmetic mean) and no value of SD will be available. Nevertheless, such an approach is often adapted by manufacturers in order to ensure internal consistency when reporting results and usually results in minimal errors.

Reporting results

See appendix for the full list of parameters that can be calculated for full quality control, assessment of breathing pattern, comparison within and between laboratories and so forth. For clinical reports it is probably only necessary to record mean \pm SD FRC_p and various key parameters for airway resistance. An X-Y plot of V_{pleth}/P_{ao} from a representative FRC manoeuvre and V_{pleth}/flow plot to show the shape of the specific resistance curve are also invaluable. Important points to remember when reporting results are: individual values of FRC should be stored, but the default set to report FRC as the mean \pm SD of results from the first three technically acceptable occlusions (where each individual value for FRC represents the mean of all data collected during one occlusion). Separate summaries of EI and EE occlusions can be presented if desired; R_{aw} , designated with appropriate suffixes to denote how it was calculated (see appendix) should be reported as the weighted mean \pm SD of as many breaths as possible (minimum 5, which will hopefully be far more in the future), together with the number of breaths the result was obtained from; according to individual preference the weighted mean \pm SD for number of breaths for sR_{aw} or sG_{aw} can also be reported.

Reference data

The published "reference" data for plethysmographic parameters in infants may not be applicable to the

current studies and should be used with great caution [3]. FRC_p should never be expressed as a ratio per unit of body length, the proposed preliminary equation for predicting FRC_{pleth} in healthy infants up to 15 months is:

$$FRC_{pleth} = 2.36L^{0.75} \times W^{0.63} \text{ (RSD 0.140)} \quad (5)$$

where L is crown heel length, (cm) and W is the body weight (kg).

The 95% confidence intervals around predicted FRC_{pleth} , from this equation are 76–132% respectively. This equation will need to be amended as further data become available. There is a relative lack of reference values for R_{aw} during the first year of life, especially with respect to any data published in recent years. New standards will need to be developed as new analytical approaches are implemented.

Future directions/controversies

Considerable further work is required to evaluate the potential usefulness of implementing some means of compensating for the thermal/humidification artefacts during R_{aw} measurements in infants without having to use a heated rebreathing bag. While the latter is certainly feasible, it requires carefully designed equipment and considerable skill on the part of the operator, thereby limiting its use to specialized laboratories. Furthermore, even when the period of rebreathing is restricted, some build up of CO_2 is inevitable, which may influence the very parameters that are under investigation.

There is currently no consensus regarding the best approach to analysing R_{aw} in infants, and further experimental work is required to provide the necessary objective evidence. However, it is generally recognized that: 1) no single value can adequately describe R_{aw} in any infant, since this parameter is strongly influenced by so many factors, including phase of respiration, lung volume and flow at time of measurements. Changes in R_{aw} through the breath are likely to be most marked in those with airway disease, and may provide important information regarding the underlying pathology; 2) the breath-to-breath variability of R_{aw} is likely to be particularly high if the algorithms relate the Δ box signal to Δ flow between specified single data points such as zero flow to 50 or 66% peak flow as has been reported in previous publications [3, 22, 23]. 3) With modern computing facilities, a better approach may be to calculate mean R_{aw} throughout the breath, and to look at relative changes in R_{aw} at high and low volumes throughout the tidal breath, together with the relationship between inspiratory and expiratory resistance at similar lung volumes. One such approach has been described previously [24–26], wherein R_{aw} can be calculated for each sampled point in order to acquire an array of values as a function of V_T throughout the breath. If the pressure/flow relationship is perfectly linear, R_{aw} *versus* V_T will yield a constant, horizontal plot, whereas if resistance rises towards EE, for example, this will be graphically evident. 4) Ideally far more breaths should be analysed than has been common in the past. This may require a new approach

regarding breath selection *etc.* 5) The use of specific resistance in infants needs to be investigated more thoroughly, together with an examination of the relationship between these various parameters. The relative reproducibility and potential clinical usefulness of the various estimations of R_{aw} also requires considerable further study [1, 17, 18].

Potentially useful methods of analysing sR_{aw} and hence R_{aw} include: 1) specific effective airway resistance (average sR_{aw} throughout breath- $sR_{aw,eff}$: the specific effective airway resistance can be calculated by dividing the integrated area of the specific work of breathing loop (tidal volume *versus* box signal) by the tidal flow/volume loop). Provided such data points are equidistant this is equivalent to regressing through all sampled data points of the specific resistance loop ($\Delta V_{pleth}/\Delta flow$ throughout the breath). Slight differences will occur when sample points are unequally distributed as may occur, for example, when rapid changes in flow with minimal volume change occur at the start of inspiration. This may result in relatively few data points over this portion of the breath even when sampling at 200 Hz.

"Effective" airway resistance ($R_{aw,eff}$) is derived from specific effective resistance by using the average lung volume during the breath. The latter is calculated as the mean FRC_p from all valid FRC measurements, plus half the V_T of the breath used to analyse R_{aw} *i.e.*:

$$V_{eff} = FRC_p + \left(\frac{V_{T,R_{aw}}}{2} \right) \quad (6)$$

so that

$$R_{aw,eff} = \frac{sR_{aw,eff}}{V_{eff}} \quad (7)$$

2) sR_{aw} at low (lv) and high (hv) volumes: additional information regarding any volume dependence of the infant's resistance may be obtained by performing such measurements at both low lung volumes (as reflected by the slope of $V_{pleth}/flow$ during late expiration and initial inspiration) and high lung volumes (*i.e.* the slope between designated flow limits during late inspiration and early expiration). 3) Resistance *versus* tidal volume: as discussed earlier, an alternative method of inspecting volume related changes in resistance is to plot R_{aw} throughout the breath against V_T [26]. 4) Relationship of initial inspiratory to end expiratory resistance: evidence of either upper airway obstruction or peripheral airway obstruction may be obtained by inspecting the relationship of initial inspiratory to end expiratory resistance. The former is likely to give a very high and the latter a very low ratio.

It should be stressed that all these approaches need considerable further evaluation before clear recommendations can be given.

Summary of recommendations

Equipment

The recommendations for the equipment include ensuring: the plethysmograph is constructed of suitable materials to ensure adequate heat exchange and also

that it is not excessively insulated. The compensation chamber should have identical thermal and mechanical characteristics as the plethysmographic chamber; frequency response is satisfactory to 10 Hz; the PNT is linear over the range of flows encountered; a low dead space, low resistive shutter is used. The combined dead space of the PNT and occlusion shutter should ideally be less than $2 \text{ mL}\cdot\text{kg}^{-1}$. The resistance of the combined apparatus should be $<20\%$ of the infant's intrinsic resistance; automated and remote control of the shutter, which is essential, as is the need for it to default to the open position in the event of any equipment or software failure; when measuring airways resistance the apparatus and the HRB incorporates servo-controlled heating elements. The HRB should be made of highly compliant but nonelastic material.

Data acquisition and signal processing

Recommendations include: a sampling rate of 200 Hz; drift correction of the box signal, which is essential when assessing the relationships between the box signal and either flow (R_{aw}) or airway opening pressure (FRC_p); establishing a representative baseline EEL before calculating FRC_p .

Data collection of functional residual capacity

The data collection recommendations include: performing measurements in the supine position while the infant is in quiet sleep; carrying out occlusion at EI, once the infant is breathing regularly with a well-established EEL; holding occlusion for at least two complete respiratory efforts to allow for accurate drift correction; repeating measurements until up to 5 (minimum 3) technically satisfactory occlusions have been obtained.

Data collection for airway resistance

The airway resistance recommendations for data collection include: switching the infant into a rebreathing bag filled with warm, humidified air/ O_2 (BTPS) at EE for up to 30 s when the box signal is stable and the infant is breathing regularly; switching the infant back to breathing air from the box, once stable pressure/flow loops are observed; flushing the bag thoroughly and repeating until at least three technically satisfactory epochs are obtained.

Calculation of the functional residual capacity

When calculating the functional residual capacity: care must be taken to apply an appropriate drift correction to the box signal, to calculate the mean slope of each respiratory effort against the occlusion (not simply the inspiratory limb) and to exclude periods of noise immediately after shutter closure and during the peaks and troughs of each respiratory tug; the volume above FRC at time of occlusion must be subtracted

from the TOGV. This requires accurate evaluation of the EEL preceding airway occlusion; all relevant dead space must be subtracted from TOGV, including that of the facemask and any transducer tubing; technically satisfactory data are essential, ensuring that only those in which box volume and airway opening pressure are in phase and have no evidence of leak or glottic closure are accepted.

Calculation of specific resistance

When calculating R_{aw} : prior to any calculations, the box signal (V_{pleth}) must be drift corrected on a breath-by-breath basis; apparatus resistance (R_{app}) should be calculated continuously and subtracted from total measured resistance; providing there are no artefacts due to changes in the humidity and temperature of the respired gas, specific airway resistance can be calculated directly from the relationship of $\Delta V_{pleth}/\Delta flow$ prior to airway occlusion; corrections must be made for the lung volume at which sR_{aw} is measured; if technically acceptable measurements of FRC_p have been obtained, values of R_{aw} , G_{aw} and specific airway conductance (sG_{aw}) can subsequently be derived, whereby: $R_{aw} = sR_{aw}/FRC_{aw}$, $G_{aw} = 1/R_{aw}$ and $sG_{aw} = 1/sR_{aw}$.

Reporting results

The following are the recommendations for reporting the results: report FRC as the mean \pm SD of the first three technically acceptable occlusions (where each individual value for FRC represents the mean of all data collected during one occlusion); R_{aw} , designated with appropriate suffixes to denote how it is calculated (see appendix) should be reported as the weighted mean \pm SD of as many breaths as possible (minimum 5, which should hopefully be far more in the future).

Reference data

Caution should be exercised when attempting to interpret results with respect to published reference data, since this may be very specific to the population studied and the equipment used.

Future work

A considerable amount of further work is required, to evaluate the validity of implementing some means of compensating for the thermal/humidification artefacts during airway resistance measurements, in infants, without having to use a heated rebreathing bag and to assess the relative usefulness of the wide variety of analytical approaches to calculating airway resistance.

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Appendix: parameters, definitions and abbreviations that can be calculated during plethysmographic measurements

Calculation of the following parameters are recommended in any automated, commercially available system for plethysmographic assessments of FRC_p and R_{aw} in infants. Use of the suggested abbreviations is recommended in order to facilitate comparisons between systems and minimize confusion when report-

Table 1. – Appendix: parameters, definitions and abbreviations

Long form	Unit	Short form	Definition
Tidal volume FRC	mL	$V_{T,FRC}$	Tidal volume preceding FRC_p . Average over the last 5 breaths pre-occlusion
tI prior to FRC	s	tI_{FRC}	Inspiratory time preceding FRC_p . Average over the last 5 breaths pre-occlusion
tE prior to FRC	s	tE_{FRC}	Expiratory time preceding FRC_p . Average over the last 5 breaths pre-occlusion
t_{tot} prior to FRC	s	tT_{FRC}	Total breath time preceding FRC_p . Calculated as $tI + tE$ over 5 breaths pre-occlusion
RR prior to FRC	$L \cdot min^{-1}$	RRFRC	Respiratory rate preceding FRC_p . Calculated from the t_{tot} -FRC parameter as $RR = 60/t_{tot}$
SD of EEL	mL	EELs	SD of EEL measured relative to the baseline EEL calculated over 5 breaths prior to each FRC occlusion manoeuvre
Stability of EEL prior to FRC_p	%	EELs%	Stability of EEL prior to FRC_p , <i>i.e.</i> EELs expressed as a % of $V_{T,FRC}$: $EELs\% = 100 \times EELs / V_{T,FRC}$
% Change in EEL	%	$\Delta EEL\%$	Change in EEL post-preocclusion, expressed as % of mean V_T prior to occlusion
Ambient pressure	kPa	P_{amb}	Ambient pressure

Table 1. – Continued

Long form	Unit	Short form	Definition
Apparatus dead space	mL	DS _{app}	Apparatus dead space including the mask
Occluded volume	mL	V _{occ}	Volume inspired above EEL at moment of occlusion
Total occluded gas volume	mL	TOGV	Total occluded gas volume, including V _{occ} and DS _{app} (including the effective dead space of the mask)
FRC _{pleth}	mL	FRC _p	Mean functional residual capacity, <i>i.e.</i> (TOGV-DS _{app} -V _{occ})
CV of FRC _p	%	FRC _p CV	Coefficient of variation (<i>i.e.</i> 100 × (SD/mean) of n accepted FRC _p manoeuvres
No. of accepted FRC _p		FRC _{p-n}	Number of accepted FRC _p manoeuvres
Change in P _{ao,occ}	kPa	ΔP _{ao}	Mean change in P _{ao} during respiratory efforts against the airway occlusion measured between 5%–95% of troughs and peaks respectively
Change in V _{pleth,occ}	mL	ΔV _{pleth}	Mean change in box volume during airway occlusion corresponding to ΔP _{ao}
Maximal inspiratory pressure	kPa	PI _{max}	Minimal absolute value in P _{ao} during inspiratory effort against the occlusion
Maximal expiratory pressure	kPa	PE _{max}	Maximal absolute value in P _{ao} during expiratory effort against the occlusion
tI occluded	s	tI _{occ}	Duration of the first inspiratory effort during airway occlusion (for use if assessing the strength of the Hering Breuer reflex). This parameter is only measured during EE occlusions. tI _{occ} is measured from the start of inspiration (taken from the tidal volume trace) immediately before an EE occlusion until the end of the first inspiratory effort, when P _{ao} starts to rise during the occluded effort.
tE occluded	s	tE _{occ}	Duration of the first expiratory effort during airway occlusion. This parameter is only measured if EI occlusion is selected. The time is measured from the start of expiration (measured from the tidal volume trace) immediately before an EI occlusion, until P _{ao} starts to fall during the airway occlusion.
HBR-EE	%	HBR-EE	Strength of Hering Breuer Reflex calculated from end expiratory occlusion as 100 × (tI _{occ} -tIFRC)/tIFRC
HBR-EI	%	HBR-EI	Strength of Hering Breuer Reflex calculated from end inspiratory occlusion as 100 × (tE _{occ} -tEFRC)/tEFRC
Apparatus resistance	kPa·L·s ⁻¹	R _{app}	Apparatus resistance
Specific airway resistance	kPa·s ⁻¹	sR _{aw}	See definition in text, which includes correction for apparatus resistance
Specific airway conductance	1/(kPa·s ⁻¹)	sG _{aw}	Specific airway conductance. Calculated as sG _{aw} = 1/sR _{aw}
V _{eff}	mL	V _{eff}	Lung volume used to convert specific effective airway resistance (see text)
V _{lv}	mL	V _{lv}	Volume to convert sR _{lv} (see text)
V _{hv}	mL	V _{hv}	Volume to convert sR _{hv} (see text)
Airway resistance	kPa·L·s ⁻¹	R _{aw}	Effective airway resistance. Calculated as: R _{eff} = sR _{eff} /V _{eff} (where V _{eff} = effective volume above FRC at time of R _{eff} analysis – see text)
Airway conductance	L·s·kPa ⁻¹	G _{aw}	Airway conductance. Calculated as: G _{aw} = 1/R _{aw}
sR _{lv}	kPa·s ⁻¹	sR _{lv}	Specific airway resistance at low lung volume (<i>i.e.</i> end inspiratory and initial expiratory values) see text
sR _{hv}	kPa·s ⁻¹	sR _{hv}	Specific airway resistance at high lung volume (<i>i.e.</i> end inspiratory to initial expiratory values, see text)
PEF during resistance	mL·s ⁻¹	PEF	Peak tidal expiratory flow during resistance measurement as weighted mean from all accepted breaths
PIF during resistance	mL·s ⁻¹	PIF	Peak tidal inspiratory flow during resistance measurement as weighted mean from all accepted breaths
No. of R _{aw}		R _{aw,-n}	Number of accepted R _{aw} breaths
CV of sR _{aw}	%	sR _{aw} CV	Coefficient of variation of sR _{aw}
Exp to ins sR _{aw} ratio		sR-E/I	Ratio of slope of end expiratory to initial inspiratory parts of the specific resistance loop, taken from above and below zero flow over a selected flow limit
Flow limit sRI	%	%V _{R,I}	Percentage of inspiratory peak flow, used for calculation of sR _{lv} and sR _{hv}
Flow limit sRE	%	%V _{R,E}	Percentage of expiratory peak flow, used for calculation of sR _{lv} and sR _{hv}
RR during R _{aw}	L·min ⁻¹	RR _{Raw}	Respiratory rate during the resistance manoeuvre. The average over all breaths used in the resistance calculation is taken. Best is calculated from 60 × (1/mean tI + mean tE)
Tidal volume R _{aw}	mL	V _{T,Raw}	Tidal volume during the resistance manoeuvres as a weighted mean

Suggested suffixes to denote specific type of analysis *etc.* (particularly during R_{aw} measurements when so many options are available): eff: effective (*e.g.* R_{aw,eff}); E: expiratory; I: inspiratory; tot: total; hv: high volume; lv: low volume; X%: assessment at specified per cent of peak inspiratory or expiratory flow (*e.g.* R50%I = R_{aw} measured at 50% PIF, whereas sG75%E would be sG_{aw} at 75% PEF); EEL: end expiratory level.

ing results. Some refer to quality control variables, which would not be reported for each individual test but which should be stored for verification purposes. All results should be displayed to at least 3 effective digits.

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