European Respiratory Society/American Thoracic Society Technical Standard on Standardisation of the Measurement of Lung Volumes - 2023 Update


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European Respiratory Society/American Thoracic Society Technical Standard on Standardisation of the Measurement of Lung Volumes - 2023 Update

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OVERVIEW

This document updates the 2005 European Respiratory Society (ERS) and American Thoracic Society (ATS) technical standard for the measurement of lung volumes [1]. The 2005 document integrated the recommendations of an ATS/ERS task force with those from an earlier National Heart, Lung and Blood Institute (NHLBI) workshop that led to the publication of background papers between 1995 and 1999 and a consensus workshop report with more in-depth descriptions and discussion. Advancements in hardware and software, new research, and emerging approaches have necessitated an update to the 2005 technical standard to guide laboratory directors, physiologists, operators, pulmonologists, and manufacturers.

Key Updates

- Emphasis on importance of linked manoeuvres for determining lung volumes after measurement of functional residual capacity (FRC)
- For standardisation of linked spirometry, the method that is expected to be achievable by most patients is recommended.
- Emphasis on importance and limitations of biological controls for quality assurance assessment
- New equipment quality control and validation recommendations, including a requirement for isothermal lung mechanical models for calibration and verification of body plethysmographs
- Emphasis on pant frequency and recommendations on measuring airway resistance using body plethysmography. Comment on panting vs tidal breathing.
- Generalised concept of multiple breath washout (MBW) beyond nitrogen
- Updates on MBW technique based on recently published technical standards
- Differentiation between inert-gas dilution equipment that use volume-based vs flow-based spirometers
- A new acceptability and grading system for assessment of the quality of lung volume measurements. Examples of tracings distinguishing manoeuvres of different grades.
- Recommendation for using Global Lung Initiative lung volume reference values
- Updates on measurement of lung volumes by imaging and other new techniques
- Data file requirements, standardised operator comments, and sequence of lung function measurements

BACKGROUND AND PURPOSE

Determination of lung volumes—measurements of functional residual capacity (FRC) with calculation of total lung capacity (TLC) and residual volume (RV)—add important diagnostic information to what can be deduced from spirometry alone [2, 3]. A reduced forced vital capacity (FVC) on spirometry may be due to a restrictive ventilatory defect, air trapping in the setting of an obstructive ventilatory defect, or the combined presence of obstructive and restrictive
defects. A reduced TLC establishes the presence of a restrictive ventilatory defect [4]. RV and FRC can help identify the cause of a reduced FVC or TLC. Lung volume measurements may also enhance the assessment of obstructive ventilatory defects through the detection of air trapping and hyperinflation.

Unlike spirometry measurement which utilises only one methodology, lung volumes can be measured using a variety of techniques. These include body plethysmography, multiple breath washout (MBW), and inert gas dilution. In health these approaches yield similar results, but results can be quite disparate in disease. In addition, lung volumes can be obtained from imaging techniques which are also briefly covered by this document.

Methods

A proposal was submitted to update the 2005 lung volumes standards by a joint ERS and ATS task force [1]. Co-chairs and members were approved by the ATS and ERS, the latter of which managed disclosure of conflicts of interest. Task force members were physicians and scientists with experience in directing pulmonary function laboratories, clinical use of lung volumes, guidelines and standards, and research with publications in relevant areas. A medical librarian (S.K.) designed search strategies related to lung volumes using medical subject headings and text words; and limited to human studies and articles with English abstracts, 2004 through August 2021 (see Supplement). Ovid databases included MEDLINE, In-Process and Non-Indexed Citations, Embase, and Cochrane Registry of Controlled Trials (CENTRAL). Literature known to the panel but not identified by the systematic literature search was also included.

At each stage of review, at least two task force members reviewed each entry for relevance by focusing on articles with information on technical performance of lung volumes rather than only clinical application, and on tests performed volitionally by adults or children. From 9,779 abstracts after the initial search, 296 were selected for review of full-text articles, yielding 77 articles. An additional 30 were hand searched (9 in main document, 21 in the supplement), which includes some articles cited in the 2005 standard.

Task force members used published data and their expertise to make modifications, additions, and deletions to the 2005 standards. A standardised survey of equipment details was created with separate sets of questions for body plethysmography, MBW, and helium dilution. ERS staff distributed and collected the surveys from manufacturers identified by the task force. The task force also reviewed equipment specifications published on the manufacturers’ websites. Survey responses and online data were not informative enough to report survey data for all specifications in this standard. Where neither data nor expertise suggested a change, prior recommendations were retained.

DEFINITIONS AND SUBDIVISIONS OF LUNG VOLUME

The term “lung volume” usually refers to the volume of gas within the lungs, as measured by body plethysmography, gas dilution or washout. In this statement, previous definitions of lung
volumes will be used (Figure 1) [5-9]. The total volume of the lung at maximal inspiration is the TLC and can be divided into subdivisions which are either volumes or capacities. The four unique lung volumes are RV expiratory reserve volume (ERV), tidal volume (V\textsubscript{T}), and inspiratory reserve volume (IRV). The lung volumes can be combined to form lung capacities which include vital capacity (VC), inspiratory capacity (IC), FRC and TLC (Figure 1).

The volume of gas inhaled or exhaled during the respiratory cycle is called the tidal volume (V\textsubscript{T}). FRC is the volume of gas present in the lung at passive end-expiration during tidal breathing, or the sum of ERV and RV.

ERV is the volume of gas that can be maximally exhaled from the end-expiratory lung volume during tidal breathing (i.e., from FRC to RV).

RV refers to the volume of gas remaining in the lung after maximal exhalation (regardless of the lung volume at which exhalation was started).

The maximum volume of gas that can be inspired from FRC to TLC is referred to as the inspiratory capacity (IC).

IRV is the maximum volume of gas that can be inhaled from the end-inspiratory lung volume during tidal breathing.

The vital capacity (VC) is the volume change at the mouth between the positions of full inspiration (TLC) and full expiration (RV). The measurement may be made in one of the following ways: 1) inspiratory vital capacity (IVC), where the measurement is performed in a relaxed manner, without undue haste, from a position of full expiration to full inspiration; 2) expiratory vital capacity (EVC), where the measurement is similarly performed from a position of full inspiration to full expiration; or 3) forced vital capacity, which is the volume of gas that is exhaled during a forced expiration, starting from a position of full inspiration and ending at complete expiration [10].

TLC refers to the volume of gas in the lungs after maximal inspiration, or the sum of all volume compartments (RV + ERV + V\textsubscript{T} + IRV). TLC is also the sum of IC and FRC or RV and VC.

**MEASUREMENT OF FRC**

The determination of FRC is the key component in the measurement of lung volumes, and can be assessed by body plethysmography, gas dilution or washout methods, or using radiography. To obtain an accurate FRC, ERV, IC, and IRV, a stable FRC should be achieved during tidal breathing. In alignment with the 2019 Spirometry standard, a stable end-expiratory tidal volume may be defined as having at least three tidal breaths with the difference between maximum and minimum end-expiratory lung volume within 15% of the tidal volume [10]. The FRC measured by plethysmography (FRC\textsubscript{pleth}) includes nonventilated, as well as ventilated, lung compartments,
and, thus, may yield higher results than the gas dilution or washout methods in some patients with certain lung diseases [11-13]. Although theoretically $FRC_{\text{pleth}}$ may be further increased by gas that is present in the abdomen, the amount of abdominal gas is small—approximately 100 mL—and even larger volumes appear to have no effect on measurement of FRC [14]. In cases of severe airflow obstruction, $FRC_{\text{pleth}}$ may be overestimated when panting rates are $>$1 Hz (60 breaths per minute) because mouth pressure underestimates the absolute change in alveolar pressure during both inhalation and exhalation [15-17]. In patients with severe airflow obstruction, bullae or emphysema, FRC is underestimated by the gas dilution or washout methods. Despite this fact, the gas dilution/washout methods are widely used because the instrumentation can be less costly. Table 1 lists advantages and disadvantages of plethysmography, gas dilution, and washout methods. Single-breath gas dilution methods as used in the determination of alveolar volume during measurement of diffusing capacity are not covered in this standard. They are more susceptible to the problem of underestimation of total lung capacity when there is regional ventilation inhomogeneity, are not linked with spirometric manoeuvres that allow determination of other lung volumes, do not primarily measure FRC, and do not include anatomic dead space. Although there is improvement in estimation of total lung capacity from the single-breath method by using total exhaled breath as noted in the 2017 ERS/ATS $DlCO$ Standard, the limited evidence available nonetheless shows underestimation [18, 19].

**DERIVATION OF LUNG SUBDIVISIONS**

No matter what technique is used to measure FRC (see sections entitled Measurement of FRC using body plethysmography, Measurement of FRC using MBW, and Measurement of FRC using helium dilution), VC and one of its subdivisions, IC or ERV, will have to be measured to calculate the TLC and RV (Figure 1). The 2005 standard detailed two methods for measuring IC or ERV after determination of FRC, followed by calculation methods unique to each method. A subsequent study found the two calculation methods were equivalent, and although one method yielded higher values for TLC and VC in those without a ventilatory defect, the differences were small and may not be clinically significant [20].

For standardisation, the method that is expected to be achievable by most patients is recommended here. Immediately after the acquisition of the FRC measurement(s) an IC manoeuvre is performed to measure the TLC in a “linked” manner (i.e. without the patient coming off the mouthpiece prior to the completion of the manoeuvres; Figure 2). The IC manoeuvre is followed by a linked slow expiratory VC (EVC) manoeuvre to RV. Care must be taken to coach patients through a slow EVC because commensurate with any degree of obstructive ventilatory defect, there is potential for air trapping and overestimation of RV with a forced manoeuvre that can cause premature dependent airway closure (Figure 3). Some patients may need to take tidal breaths immediately after the determination of FRC, and this is acceptable as long as they remain on the mouthpiece. The reported value for the FRC is the mean of technically acceptable FRC measurements used for the calculation of TLC. The TLC is the mean of the sums of technically
acceptable FRC values and linked IC manoeuvres. The RV is the reported value for TLC minus the largest VC measured. While recognising that manufacturers currently may have recommendations for measurement of static lung volumes without linked manoeuvres, it is recommended that all methods link the spirometry manoeuvres with the FRC measurement to calculate TLC and/or RV.

Linked spirometry is optimal. However, some patients may have difficulty with linked spirometry after many minutes on the mouthpiece during measurement of FRC by MBW or helium dilution. In these cases, unlinked spirometry is an alternative after reestablishing a resting FRC with tidal breathing. Results that incorporate unlinked manoeuvres should be reported with caution (useable rather than acceptable). Differences in FRC between linked and unlinked manoeuvres are likely to be small relative to the TLC which is often the primary outcome of the test. Unlinked spirometry is not a recommended option for plethysmography.

Recommendations for the measurement of IC and unforced VC (slow vital capacity, SVC) are presented in the document on the standardisation of spirometry [10]. Repeatability of the IC and ERV, which are used in computing TLC and RV, are determined in part by the repeatability of FRC which is covered below.

**GENERAL PATIENT PREPARATION**

The patient’s age, height, and sex are used in the reference equations to calculate predicted values. Age should be expressed in years to one decimal point. Height should be measured in centimeters to one decimal place, without shoes, and with the back flat against a surface ideally using a stadiometer (see Supplement). For patients with a deformity of the thoracic cage, such as kyphoscoliosis, the arm span from fingertip to fingertip, or ulna length, can be used in regression equations which provide adjustments for age and sex to estimate height. Details are available in the 2019 ERS/ATS Standardisation of Spirometry Technical Statement [10]; diagrams detailing best practices can be found in the Supplement. Technical comments should be available on the report when standing height cannot be measured but is instead estimated, for example: ‘Predicted values have been calculated using an estimate of standing height and should be used with caution.’ Weight should be measured to the nearest 0.5 kg, as plethysmographic systems use weight to calculate body volume in the calibration software. Weight is also used as a guide to anatomical dead space in some systems but is inferior to direct measurement via the Fowler method [21].

Activities that should be avoided before testing and instructions on withholding medications are included in the Spirometry 2019 update. The operator should record the type and dosage of any (inhaled or oral) medication that may alter lung function and when the drugs were last administered. The decision to avoid long- and short-acting bronchodilators is a clinical one, dependent on the question being asked. Patients should be asked to wear loose-fitting clothing
and refrain from eating a large meal or drinking large volumes of liquid prior to testing. Dentures should normally be left in place; however, if they are loose, they may interfere with performance and should be removed. Special considerations in children are covered in recent statements on pulmonary function testing [10, 22]. Protection of patients and staff from infection through pre-testing patient evaluation, cleaning of testing rooms and equipment, and management of the laboratory environment are covered elsewhere [23].

SEQUENCE OF LUNG FUNCTION MEASUREMENTS

Previous standards suggested that the order for performing lung function tests should consider the optimum workflow in the laboratory, potential influences of one test on another, the ability of the patient to undertake the test, and that the order should be kept constant to avoid introducing unanticipated variability to test results [24]. There is no recommendation for or against use of a bronchodilator prior to measurement of the transfer factor of the lung for carbon monoxide (Dlco) [18]. An example order of performing tests is: Spirometry, Static lung volumes, Inhalation of bronchodilator agent (if used), Diffusing capacity, repeat Spirometry, and repeat Static lung volumes (if required).

It is recommended that Dlco measurements be made before any multi-breath nitrogen washout tests as residual oxygen may result in underestimation of Dlco [24]. Therefore, an alternative order of performing lung function tests would be: Spirometry, Dlco, Multiple breath nitrogen washout test, Inhalation of bronchodilator agent (if used), repeat Spirometry.

MEASUREMENT OF FRC USING BODY PLETHYSMOGRAPHY

Introduction and theory
The term thoracic gas volume (TGV or VTG) refers to the plethysmographic measurement of intrathoracic gas at the time of airflow occlusion. The volume is the compressible gas within the thorax. The term FRCpleth refers to the FRC during relaxed tidal breathing prior to measurement of TGV as obtained by applying a correction if needed for any difference between TGV and FRC. Plethysmographic measurements are based on Boyle's Law, which states that, under isothermal conditions, when a constant mass of gas is compressed or decompressed, the gas volume decreases or increases and gas pressure changes such that the product of volume and pressure at any given moment is constant [13, 14]. More detailed reviews of the theory are available [25].

Equipment
The changes in thoracic volume that accompany a compression or decompression of the gas in the lungs during respiratory manoeuvres can be obtained using a constant volume body plethysmograph by measuring the changes in box pressure. The body plethysmograph is a cabin with a total cabin volume of 700-1,200 L. A larger cabin may be needed for very tall or obese patients. Some large cabins are accessible for patients in a wheelchair. A bidirectional intercom should be available for communication between patient and operator.
A transducer capable of measuring mouth pressure ≥ ± 5 kPa (≥ ± 50 cmH2O), with a flat frequency response of more than 8 Hz, is essential. All nine current manufacturers of plethysmography equipment surveyed reported that the mouth pressure transducer could measure this range and three reported meeting or exceeding the minimum frequency response. Flow measuring devices that are used for the measurement of lung volumes and maximal inspiratory and expiratory volumes should meet published standards for the accuracy and frequency response of spirometric devices [10]. The transducer measuring changes in the cabin pressure must be capable of accurately measuring a range of ± 0.02 kPa (± 0.2 cmH2O) [26]. Thermal drift may give rise to a pressure change of as much as 0.1 kPa (1 cmH2O), which may necessitate a larger working range of the transducer [13]. Equipment from eight of nine manufacturers surveyed meet this larger range for cabin pressure measurement. Cabin pressure transducer accuracy and resolution should be maintained across the measurement range. Manufacturers’ responses for cabin pressure transducer accuracy and resolution varied and warrant standardised reporting. A time constant of 10 s (range 5-25 s) for a controlled leak (which minimises slowly occurring pressure changes) is ideal. Of the nine current manufacturers surveyed, five reported a value of ≤ 10 s. Thermal drift due to temperature changes in the interior of the plethysmograph is common to all types of equipment and can be detected and compensated for from the volume–pressure plot during an occlusion showing a systematic difference in slope between compression and expansion [13].

Manufacturers should state the frequency response of their plethysmographic systems and provide instructions for the user on how to verify it. The verification of frequency response is most commonly accomplished by the application of a sinusoidal volume signal, where the frequency can be varied [13]. It is generally recommended that the minimum adequate frequency response should be five times the frequency of the signal being measured. For a pant at 1 Hz, this means accuracy of the signal at 5 Hz. For panting frequencies slightly above 1 Hz, the minimum acceptable frequency response is 8 Hz.

**Patient preparation**
The measurement procedure must be thoroughly explained, demonstrated, and practiced with the patient. This must include practicing: 1) mouthpiece and nose clip placement 2) panting by putting the hand over the mouth 3) supporting the cheeks i.e., flat of the hands against the cheeks, without raising the arms 4) tight lip seal throughout the measurement and specifically while shutter is closed and 5) closing the door. Supporting the cheeks is particularly important in the setting of airflow obstruction where it reduces but does not eliminate the impact of higher panting frequencies [17]. For patients with claustrophobia, it is important to explain that the door can be released at any time from both the outside and inside.

**Measurement technique**
The measurement technique requires the following steps:

1) Equipment should be:
a. turned on and allowed an adequate warm-up time (as specified by the manufacturer)

b. set up for testing, including calibration, according to manufacturer's instructions. During calibration and use, rapid changes in room pressure and vibrations should be avoided (e.g., doors shutting abruptly, changes in room air currents from HVAC and HEPA systems). Gusty winds and direct sunlight may also affect measurements.

c. adjusted so that the patient can sit comfortably in the cabin and reach the mouthpiece without having to flex or extend the neck.

2) The plethysmograph door is closed, and time is allowed for the thermal transients to stabilise (approximately 30 s – 2 min) and the patient to relax.

3) The patient is instructed to attach to the mouthpiece (flange-type preferred), and breathe quietly until a stable end-expiratory lung volume, i.e., FRC is reached (usually 3–10 tidal breaths; see above Measurement of FRC).

4) The shutter is closed at or near end-expiration for ~2–3 s, during which time the patient is instructed to perform a series of gentle pants against the closed shutter (~ ± 1 kPa (~ ± 10 cmH2O)) at a frequency between 0.5 and 1.0 Hz, approximately 30-60 pants per minute. Panting frequencies of > 1.5 Hz may lead to overestimation of FRC. This effect increases as obstruction worsens. Panting frequencies of < 0.5 Hz may cause problems with the controlled leak of the body plethysmograph system. Acceptable panting manoeuvres should be recorded (i.e., a series of 2-3 almost superimposed straight lines separated by only a small thermal drift on the pressure–volume plot; Figure 4).

5) Next, the shutter opens and the patient performs a linked IC manoeuvre followed by an EVC (Figure 2). Patients with severe dyspnoea may have difficulty performing linked spirometry immediately after closed shutter panting. To overcome this, the patient can be instructed to stay on the mouthpiece and take two or three tidal breaths after the panting manoeuvre, prior to performing the linked IC and EVC manoeuvres.

6) The operator must review the placement of tangent lines on the panting loops. Adjust the tangent lines only if the software placement appears to be in error. Tracings for plethysmograph tests should be shown graphically in the report to aid quality assessment [27]. Similarly, the operator must verify automatic adjustment for differences between VTG and FRCpleth on the spirometer tracing. Panting frequency should also be reported.

7) Measurement of airway resistance must not be performed during the same manoeuvre performed to measure lung volumes because the optimal panting frequencies are different and increased time on the mouthpiece increases opportunity for leak which can compromise accurate measurement of lung volumes (see Supplement).
Quality control

The accuracy of the flow and volume output of the mouth flow-measuring device should comply with the recommendations made in the spirometry 2019 document [10].

The mouth pressure transducer should be physically calibrated daily or prior to use. The plethysmograph signal should also be calibrated daily, using a volume signal of similar magnitude and frequency as the respiratory manoeuvres during testing. Calibration must be performed more frequently when temperature or pressure are changing (e.g., twice a day).

A validation of accuracy using a known volume must be performed monthly, when new software uploaded, or a problem is suspected. This can be carried out using a “model” lung or container of known volume, ideally of two different sizes [13, 28]. Filling a flask with thermal mass (e.g., copper wool) and using the proper frequency of air movement (0.5-1 Hz) are essential in order to simulate the isothermal conditions within the lung; care should be taken to adjust the calculated volumes to ambient (or model) temperature and saturated conditions, rather than to body temperature and ambient pressure, saturated with water vapour (BTPS) conditions, during the calculations. If a person is required to be in the cabin during use of the model lung, their anthropomorphic data should be entered into the software to get accurate measurements. The accuracy of adult plethysmographs in measuring the gas volume of the container should be ±50 mL or 3%, whichever is greater, based on a mean of five determinations [13].

At least monthly, or whenever errors are suspected, two healthy non-smoking reference subjects (biological controls) should undergo body plethysmography. Previously established baseline data from the biological controls should have a coefficient of variation of < 5% for both FRC and TLC. Values that differ significantly from the baseline means on the same subject suggest errors of measurement. A suggested threshold above which the difference is significant is 2 standard deviations above the mean, with the standard deviation calculated from the baseline data points. A large multi-laboratory study of repeat measurements found that this threshold is approximately 4% for TLC and 7% for FRC [29]; tighter standards can be adopted at the cost of more frequent false alarms that suggest equipment malfunction. Biological controls can identify problems missed during in vitro testing such as if an incorrect mouthpiece is being used [30]. If the operator is a biological control, they can provide acute evaluation of equipment suspected to have a problem during patient testing. The task force recognises that although experience supports the value of biological controls, evidence for the practice is lacking, there are challenges with variability (e.g., ageing, low vs high natural individual variability), a range of values tested that do not include extremes of disease, laboratory efficiency, timely analysis of data, turnover and availability of staff, and concerns with privacy if staff serve as biological controls (see Supplement for data analysis spreadsheet).
A validation process for onboarding new, repaired equipment, or significantly updated software has been defined in the online Supplement. This process assists the laboratory management team in identifying bias or shifts in clinical results related to an equipment change.

Calculations
The calculation of VTG is based on Boyle’s Law, which states:

\[ P_{\text{atv}1} \times VTG_1 = P_{\text{atv}2} \times VTG_2 \]  

(1)

\( P_{\text{atv}1} \) and \( VTG_1 \) are the absolute pressure and lung volumes before the compression/decompression manoeuvre, and \( P_{\text{atv}2} \) and \( VTG_2 \) are the absolute pressure and lung volumes after the manoeuvre. Water vapour pressure needs to be subtracted from all pressures, because it does not behave as a compressible gas in that its partial pressure is determined only by temperature, but this is not shown for the sake of simplicity. Expressed as a change from the baseline, the equation becomes:

\[ VTG = \left( \frac{\Delta V}{\Delta P} \right) \times P_{\text{atv}2} \]  

(2)

Since the panting manoeuvre is intended to occur with small changes in pressure around barometric pressure (\( P_B \)), the simplified and widely used version is:

\[ VTG = \left( \frac{\Delta V}{\Delta P} \right) \times P_B \]  

(3)

\( \Delta V/\Delta P \) represents the slope of the simultaneous changes in body volume, which, in a pressure plethysmograph, are the tiny changes in pressure within the box, calibrated to reflect changes in the volume of the subject versus the change in pressure at the mouth. When a rapid inspiratory manoeuvre is performed, the complete version must be used, as follows:

\[ VTG = \left( \frac{\Delta V}{\Delta P} \right) \times P_{\text{atv}2} \times \left( \frac{P_{\text{atv}1}}{P_B} \right) \]  

(4)

If the panting manoeuvre begins with a \( P_{\text{atv}1} \) that is different from \( P_B \), as occurs if the occlusion takes place at a volume other than FRC, the volume will need to be corrected to FRC, but \( P_{\text{atv}1} \) will also need to be corrected for \( P_B \). Details of the complete derivation of the equations are given in both a web-based document and background paper [13].

The underlying assumption of the technique is that the pressure–volume changes in the body are isothermal, and any heat generated by compression is instantaneously lost to the surrounding tissue. However, changes in pressure and volume within the plethysmograph are assumed to be adiabatic (i.e., there is insufficient time for heat exchange to occur between the air within the plethysmograph and either the walls or the subject during the decompression and compression manoeuvre). For panting frequencies on the order of 1 Hz, this assumption is valid. However, slow decompression manoeuvres where the subject is occluded at end-expiration and the pressure–volume changes occur with the normal respiratory effort are to be discouraged, since the time course may allow for heat exchange within the plethysmograph. This would alter the
pressure–plethysmograph volume calibration. This would not be a problem if the subject made a rapid inspiratory effort, but the complete version of Boyle's Law should be used [13]. Along the same line, it is customary to subtract the volume of the apparatus between the mouth and the occluding valve from the TGV. However, decompression and compression of this volume are not isothermal, and if the volume is large in relation to TGV due to an excessively large filter, for example, errors will be introduced. In other words, efforts should be made to minimise the volume between the occluding valve and the patient.

**Body plethysmography in children**

In most children aged 3 or older who successfully completed spirometry, body plethysmography is possible. This requires staff specially trained to work with children. In one study, 70% of young children between 3 and 7 years who successfully performed spirometry were able to tolerate occlusions and sufficiently performed FRC measurements in the body plethysmograph. During each closed shutter procedure two to three breathing efforts were performed [31]. In order not to disturb the pressure measurements by dangling of the feet, it is important to adjust the height of the seat and use a footrest if necessary. If a footrest is used, box calibration should be performed with the footrest inside the box.

**MEASUREMENT OF FRC USING MULTIPLE BREATH WASHOUT**

**Introduction and theory**

The multiple breath inert gas washout technique (MBW) is based on washing out an inert tracer gas from the lungs over multiple tidal breaths. This tracer gas can either be an endogenous gas (e.g., N₂) washed out by breathing 100% oxygen, or an exogenous gas (e.g., sulfur hexafluoride) washed out using room air. The initial alveolar tracer gas concentration and the amount of tracer gas washed out can then be used to calculate the lung volume at the start of washout (the breath immediately preceding the washout). FRC measured by MBW (FRC_{MBW}) represents the lung volume at end of expiration in direct communication with the airway opening.

While historical versions of the test were based on a set time period (e.g., 7 min), the current consensus guidelines [32] recommend an end of test threshold when the end-tidal tracer gas concentration reaches below 1/40th of the start concentration, which corresponds with the threshold used to calculate the lung clearance index.

Additional details and literature regarding various inert gas washout techniques and the calculation of ventilation inhomogeneity indices are available in the ATS/ERS Consensus Statement and ATS Preschool Technical Statement for MBW testing [32, 33].

**Equipment**
Flow analysers (e.g., pneumotachographs, ultrasonic flow meters, turbines, etc.) incorporated into the breathing circuits to measure gas flows should have an instantaneous flow accuracy within 5% across the range of flows encountered during clinical testing and volume accuracy within 3% using a precision calibration syringe [32]. In young children, tidal volume accuracy should be within 3% or 5 mL, whichever is greater [33].

Gas analyser properties should ensure a linear and accurate gas signal. End-tidal tracer gas concentrations should be within ≤ 1% of the tracer gas concentrations at the start of the washout (e.g., ± 0.8 at 80% N₂) and within 5% of the tracer gas concentrations at the end of test criteria (e.g., ± 0.1 at 2% N₂). An analyser rise time of < 100ms to 90% of the target gas concentration is recommended across all age groups. The system should have a sampling rate of ≥ 100 Hz per channel for flow and gas concentration measurements (met by all nine current manufacturers of MBW equipment surveyed). In systems utilising CO₂ and O₂ analysers for indirect measurement of N₂, the same requirements noted for N₂ analysers should be met for the calculated N₂ gas concentrations. Manufacturers and users should be aware of the potential for cross-sensitivity between CO₂ and O₂ analysers, which in one system lead to overestimation of FRC and was corrected by a software update [34, 35]. Of nine current manufacturers of MBW equipment surveyed, four meet the above specification for direct or indirect measurement of N₂ tracer gas concentration and four only reported O₂ analyser accuracy of within 1% and CO₂ accuracy within 0.1%.

Flows and integrated volumes should be reported at BTPS (body temperature, pressure, saturated with water). Signals for flow and gas concentrations should have a temporal alignment accuracy within 10 ms across the duration of the entire washout. Dynamic flow and viscosity dependent delay synchronisation is recommended for testing in young children because the high variability in breathing pattern influences delay between the flow and gas concentration signals. The total equipment dead space should be minimised to < 2 mL.kg⁻¹. Equipment-related resistance should be minimised to avoid the effects on breathing pattern and FRC during testing.

**Patient preparation**

The measurement procedure should be thoroughly explained, demonstrated, and practiced with the patient. This must include practicing: 1) mouthpiece and nose clip placement, 2) tight lip seal throughout the measurement, and 3) relaxed tidal breathing. A flanged or scuba-like mouthpiece or face mask can assist with preventing leaks. If tolerated, patients should not breathe supplemental oxygen for ≥ 10 min prior to an MBW manoeuvre—the operator should confirm that exhaled nitrogen is 78% prior to a manoeuvre and wait additional time if it is not. The patient should be asked if they have a perforated eardrum—if so, an earplug should be used.

**Measurement technique**
The measurement technique should adhere to the following steps:

1) The equipment should be turned on and allowed an adequate warm-up time and set up for testing including spirometer and gas calibrations, according to manufacturer’s instructions.

2) The patient is instructed to breathe regular tidal breaths without sighs, cough, or apnea. Children should perform relaxed tidal breathing whereas adults can be encouraged to perform fixed volume tidal breathing (e.g., 1 L).

3) An adequate time should be allowed (~30-60 s) before the washout phase to permit the patient to become accustomed to the apparatus and ensure a stable end-tidal expiratory lung volume (see Measurement of FRC above).

4) Switching to the washout phase:
   (a) For N₂MBW, the patient breathes room air during a pre-washout phase before being switched to 100% oxygen to washout the resident N₂ gas.
   (b) For exogenous gas MBW, the patient breathes an inert tracer gas mixture during a wash-in phase until an equilibrium in gas composition is reached between the lung and the tracer gas mixture. The patient is switched to room air to washout the exogenous tracer gas.
   (c) The switch to 100% oxygen (N₂MBW) or room air (exogenous gas MBW) should occur at the stable FRC.

5) The tracer gas concentration is monitored during the washout. A change in inspired tracer gas or sudden large increases in expiratory tracer gas concentrations can indicate a leak and the test should be stopped. A typical profile is shown in Figure 5. If end-tidal CO₂ is available, it should remain in the range of 4-6% to exclude significant hypo/hyperventilation. MBW is a tidal breathing test that should report FRC in ventilated regions of the lung. Breathing deviations outside of this (both immediately before and during washout) should be avoided to prevent the release of trapped gas from under-ventilated regions, which can affect the measurement and repeatability of FRC [32].

6) The washout is complete when the end-tidal tracer gas concentration is below 1/40th of the starting concentration for at least three consecutive tidal breaths.

7) Once measurement of FRC is complete, the patient is instructed to perform a linked manoeuvre as described in Derivation of Lung Subdivisions above.

8) A waiting period of at least twice the washout time is recommended between manoeuvres. Longer waiting periods may be required in patients with severe obstructive or bullous disease [36].

**Quality control**

Before each patient is tested, the concentration of tracer gas should be within 0.5% of the expected baseline reading (e.g., 78.08% for N₂ in ambient air). The accuracy of the flow and volume output of the flow measuring device should be confirmed at least daily with a calibrating syringe. A two-point calibration of gas analysers is recommended prior to each testing day.
Testing of biological controls should be performed monthly and whenever an error is suspected; see plethysmography section for guidance on using biological controls.

Calculations

FRC\textsubscript{MBW} is computed from the following equation:

\begin{equation}
\text{FRC}_{\text{MBW}} \times \text{Fet}_{\text{start}} = (\text{FRC}_{\text{MBW}} \times \text{Fet}_{\text{end}} + \text{net volume of inert gas exhaled})
\end{equation}

Solving for FRC\textsubscript{MBW}, this becomes:

\begin{equation}
\text{FRC}_{\text{MBW}}^* = (\text{net volume of inert gas exhaled}) / (\text{Fet}_{\text{start}} - \text{Fet}_{\text{end}})
\end{equation}

where Fet is the concentration at end-tidal volume of the tracer gas, at the start (Fet\textsubscript{start}) and end (Fet\textsubscript{end}) of the MBW measurement. The net volume of tracer gas exhaled is calculated as the sum of the integral products of exhaled volume and gas concentration for each washout breath. *FRC\textsubscript{MBW} includes the volume of the equipment dead space between the sensor and the patient, which is subtracted, and the result corrected to BTPS conditions. Correction for potential diffusion of tissue N\textsubscript{2} into the lung is no longer recommended [32].

**MEASUREMENT OF FRC USING HELIUM DILUTION**

**Introduction and theory**

The method for measuring lung volumes is based on the mixing and equilibration of the resident gas in the lung with a known volume of gas containing helium. Helium is inert and insoluble so that negligible amounts cross the alveolar membranes into the lung tissue and blood. The test gas typically consists of a concentration of helium and oxygen. During the test the helium concentration falls progressively, stabilising once mixing is complete. During rebreathing the CO\textsubscript{2} is absorbed and oxygen is added continuously to maintain a constant overall volume of the system (equipment and the lungs).

The lung volume (FRC\textsubscript{He}) at the time the subject is connected to the spirometry apparatus of a known volume (V\textsubscript{app}) and helium fraction (F\textsubscript{He1}) is calculated from the helium fraction at the time of equilibration (F\textsubscript{He2}) as follows:

\begin{equation}
\text{V}_{\text{app}} \times \text{F}_{\text{He1}} = (\text{V}_{\text{app}} + \text{FRC}_{\text{He}}) \times (\text{F}_{\text{He2}})
\end{equation}

\begin{equation}
\text{FRC}_{\text{He}}^* = \text{V}_{\text{app}}(\text{F}_{\text{He1}} - \text{F}_{\text{He2}})/\text{F}_{\text{He2}}
\end{equation}

FRC\textsubscript{He}^* includes the dead space of the equipment and mouthpiece, which is subtracted, and the result corrected to BTPS conditions.

**Equipment**

There are typically two main equipment configurations used to perform this test: The first was described in detail in the 2005 standard utilising a volume displacement spirometer ≥ 8 L, a mixing fan, CO\textsubscript{2} absorber, O\textsubscript{2} and helium supplies, a gas inlet and outlet, and a water
vapour absorber in line with the helium analyser. Figure 6 is an example of this configuration with the equipment connected to the patient via a circuit and tubing. The spirometer is filled with a known concentration of Helium (~10%). Oxygen is added and mixed using a fan. Any drift because of CO₂ absorption and O₂ consumption is observed in the spirometric baseline trace and can be corrected by the continuous addition of O₂. The time course of helium equilibrium in a normal subject and a patient with COPD is presented in the spirogram and the helium concentration versus time graph.

Another commonly available configuration utilises a flow sensing spirometer (pneumotachograph), with a rebreathing bag, CO₂ absorber, mixed O₂ and helium supply, a gas inlet and outlet, an oxygen compensation switch, and a water vapour absorber in line with the helium analyser (Figure 7). Exact gas concentrations (generally 9-14% helium, 21% oxygen, balance air) from a certified medical gas cylinder are added to a rebreathing bag from which the patient will inhale and exhale until equilibration is reached, as determined automatically by the measuring system. The deadspace volume of a pneumotachograph is less than that of a volume displacement configuration e.g., ~1 L instead of ~4 L. The method of gas mixing in this configuration varies by manufacturer. Some manufacturers use a fan to mix the gas prior to and during the helium wash-in phase. Others report that mixing is performed by the subject's tidal ventilation instead of using a fan. Equilibration is also assisted by the gas sampling that comes from the bag, through the analyser and then returned to the bag. The oxygen level is kept constant by injecting oxygen into the circuit when oxygen falls below the threshold level. A stable baseline indicates no dilution of oxygen in the circuit and hence the initial bag volume is maintained. The CO₂ is removed both on expiration and on inspiration using a chemical absorber e.g., soda lime. It is useful to note that an increase in temperature may result from the patient breathing across the CO₂ absorber leading to production of heat and water vapour and can result in water droplets in the rebreathing bag. This may require the use of single-use rebreathing bags. The spirometer should comply with the latest volume measurement standard [10]. Circuit resistance including mouthpiece and filter should be < 0.05 kPa/L/s. The volume of bacterial filters should be minimised (ideally < 100 ml). The dead space details should be available from the manufacturer. The 2005 standard describes helium analysers, gas sampling and absorber requirements.

**Patient Preparation**
The procedure is explained, demonstrated, and practiced, emphasising the need to avoid leaks around the mouthpiece during the test with a tight lip seal and to use a nose clip. Use of a flanged mouthpiece will assist with preventing leaks. The patient should be asked if they have a perforated eardrum—if so, an earplug should be used.

**Measurement technique**
Specific details of procedures will vary with different types of equipment and degrees of automation [37], but the basic procedure is as follows.

1) The equipment should be turned on and allowed an adequate warm-up time and set up for testing including spirometer and gas calibrations, according to manufacturer's instructions.
2) The patient breathes on the mouthpiece to achieve a stable tidal expiratory breathing pattern, which typically takes between ~30–60 s to become accustomed to the apparatus (see Measurement of FRC above).

3) The patient is connected to the test gas at the end of a normal tidal expiration.

4) The patient is instructed to breathe regular tidal breaths. Continuous measurement of the O₂ concentration ensures a satisfactory O₂ supply and provides a means to adjust the output of thermal-conductivity helium analysers for the effect of different O₂ concentrations. Irregular breathing during dilution may affect the measurement and repeatability of FRC in the setting of heterogeneous ventilation. In some systems, irregular breathing may impact the O₂ supply and thereby potentially affect the measurement of FRC by changing helium concentration through a change in circuit volume.

5) Continuously monitor the percentage helium concentration and equilibration graph for potential leaks (Figure 8). A sudden drop in helium indicates a system leak and will result in an overestimation of FRC. Helium equilibration is considered to be complete when the change in helium concentration is < 0.02% for 30 s. The test rarely exceeds 10 min, even in patients with severe ventilation inhomogeneity [37].

6) Once the helium equilibration is complete, the patient is disconnected from the test gas and measurements of ERV and IC are linked to the FRC measured as described in “Derivation of Lung Subdivisions” above.

7) A waiting period of at least twice the dilution time is recommended between manoeuvres. Longer waiting periods may be required in patients with severe obstructive or bullous disease.

Quality control
Before each patient is tested, the following items should be checked: status of all CO₂ and water absorbers; operation of the circuit fan if applicable (assessed by listening); and the baseline stability of helium and volume signals. The reliability of the CO₂ and water absorbers should be checked before each test (either from visual inspection, or by replacing the absorbent after a specified number of tests or accumulated minutes of equilibration time).

Systems that can have gas filling volume checks should be checked for leaks at least once per month, and after tubing or canister changes. The stability of the helium analyser should be confirmed weekly (it should not drift > 0.02% in 10 min—one out of four current manufacturers of helium dilution equipment surveyed reported a 10 min drift of 0.01%). The temperature should be validated as described previously [10]. Monthly testing of biological controls is recommended and useful, in that it tests not only the equipment, but also the procedures used by the operators; see plethysmography section for guidance on using biological controls.

Calculations
Providing the subject is connected to the spirometer at FRC, FRC₇é can be calculated from the previously stated equations (included in the introduction and theory of the measurement of FRC using helium dilution). With regards to corrections in calculating FRC₇é, the following points should be considered.
1) FRC\textsubscript{He} is determined at a condition between ATPS and BTPS and should be corrected to BTPS.
2) Correction factors for N\textsubscript{2} excretion during the helium equilibration, and corrections for helium concentration when the respiratory quotient differs from 1.0 can be ignored [37].
3) With regards to switching errors, in practice, patients are not always at FRC when they are switched into the spirometer circuit. Corrections for this are typically made automatically from the spirometer trace (see Supplemental Figure 5), but it is still preferable for continuous recordings of spirometry to be available so the computer-derived adjustments for switch-in errors can be confirmed (or edited) by the operator.

**MEASUREMENT OF LUNG VOLUMES USING IMAGING TECHNIQUES**

Physiologic tests are preferred to investigate a suspected restrictive disorder or hyperinflation, but in some situations including research, imaging may be the only source of lung volume information.

Volumes derived from imaging techniques preferably done in the upright position include thoracic cage volume, total lung volume, lung tissue volume, and air volume—the latter is most comparable to the results from normal persons using the physiologic techniques described above. While imaging techniques can provide subdivisions of total lung capacity including FRC and RV with more extensive coaching and pairing with spirometry, typically measurements are made only on images obtained at maximal inflation. In subjects with a limited ability to cooperate, radiographic lung volumes may be more feasible than physiological measurements. However, the extent of lung inflation at the time of image acquisition, body position, and image analysis technique influence the measurements and are essential to define. Further consideration of these details and specific imaging methods is provided in the online Supplement.

**REPEATABILITY**

The goal is to obtain at least three acceptable FRC\textsubscript{pleth} values that agree within 5% (i.e., difference between the highest and lowest value divided by the mean is ≤ 0.05). If there is a larger deviation, additional values should be obtained, until three values agree within 5% of their mean. Patient fatigue may limit the number of manoeuvres. Results with repeatability exceeding 5% may still be of use.

For MBW and helium dilution, operators should strive to obtain at least two technically acceptable trials [37, 38]. FRC\textsubscript{MBW} and FRC\textsubscript{He} should be within 10% of the mean of all acceptable or useable trials (i.e., difference between the highest and lowest value divided by the mean is ≤ 0.10). Tidal breathing is likely to be variable in young children (< 7 years) and more lenient test repeatability criteria are recommended [32, 33].
ACCEPTABILITY AND GRADING

Task force members considered whether to grade individual reported lung function indices as in the 2019 Spirometry Standard or separate manoeuvres as in the 2017 DlCO Standard. The conclusion was to provide a practical classification of FRC and linked spirometry manoeuvres—acceptable (meeting all quality criteria), useable (reported and used with caution), not useable or acceptable (reject: consider not reporting)—which combined with repeatability contribute to grading systems for the lung volume test. These grading systems can provide a level of confidence in the accuracy of lung volume measurements. The decision to grade the lung volume test rather than individual reported indices or separate manoeuvres was based on these considerations: 1) a lower quality of the linked spirometry affects multiple indices simultaneously (e.g., VC, RV, and TLC) and it is difficult to have more or less caution about one index versus another, 2) the quality of the indices is related through shared dependence on the quality of the FRC measurement followed by linked spirometry, and 3) the FRC is seldom used clinically by itself and so there is less of a need to grade it separately as there is for the FVC and FEV\textsubscript{1}. Separate acceptability and grading systems are given for different methods of measuring lung volumes because 1) each method has unique technical considerations for evaluating quality, 2) the different lung volume methods are reported to have different repeatability standards, and 3) for MBW, from which pulmonary function indices other than lung volumes are also derived, a previously proposed and evaluated grading system provided key criteria [38].

The classification and grading criteria should be incorporated into the software to reduce the implementation burden and potential for error. The acceptability and grading criteria are not validated but are an attempt to codify published data and task force members’ experience in what is achievable and best practice, with guidance from recommendations in other statements [10, 18, 32, 37, 39]. The proposed system does not preclude the use of reasonable alternatives such as removing criteria related to stability of pre-shutter closure/pre-switch-in end-tidal lung volume if RV and TLC are the only variables of interest and only linked spirometry is performed. The overriding goal of the operator must be to always achieve the best possible testing quality for each patient.

Table 2 lists acceptability criteria for the measurement of FRC\textsubscript{pleth}. Table 5 lists acceptability criteria for the linked spirometry manoeuvre. The quality of the FRC\textsubscript{pleth} manoeuvre, quality of the linked spirometry manoeuvre, and the repeatability of the measurements determine the overall grade of a testing session (Table 6). Grades D, E and U (useable) tests are reported but interpreted and used clinically with caution.

For MBW and helium dilution, acceptability criteria are listed in Tables 3 and 4. All MBW and helium dilution measurements with leak should be excluded. MBW measurements should be visually inspected for large deviations in breathing pattern that could influence results. Significant deviations (sighs, coughs, very small breaths, apneas) in tidal breathing immediately prior to and at the start of the washout will likely influence FRC results and these manoeuvres should be terminated immediately in order to collect additional attempts [38, 40-42]. A separate grading system is presented for MBW and helium dilution in Table 7 because it is not easy to obtain
multiple acceptable manoeuvres. Difficulty in maintaining a very steady breathing pattern during washout and dilution is expected to frequently yield useable rather than acceptable manoeuvres. This grading system deviates from that published for MBW [38] but is intended to be clinically useful and consistent across all methods in this standard—alternatives may be more appropriate in research settings.

REPORTING

Selection of manoeuvres
The expected higher within-visit variability of lung volume manoeuvres compared to within-visit variability of spirometry manoeuvres and risk of underestimation and overestimation of lung volumes supports averaging of lung volume results prior to reporting. If two or more acceptable manoeuvres that meet the best FRC repeatability criteria in Tables 6 and 7 (5% for body plethysmography and 10% for MBW and helium dilution) are obtained, these and their associated spirometry manoeuvres should be used to calculate and report FRC and other lung volumes per Derivation of Lung Subdivisions above. If the operator cannot obtain at least two acceptable and repeatable FRC manoeuvres, all manoeuvres with acceptable or useable FRC and spirometry, and that meet the least stringent FRC repeatability (10% for body plethysmography and 25% for MBW and helium dilution), should be used. If three or more manoeuvres (e.g., 1 acceptable and 2 useable) are considered and the least stringent FRC repeatability is not met, the manoeuvre with the largest difference from the mean FRC should be discarded with its associated spirometry; FRC repeatability is then recalculated and additional manoeuvres discarded in a similar manner until the least stringent repeatability is met. If two manoeuvres that are acceptable or useable do not meet the least stringent FRC repeatability, specific concerns about a manoeuvre should inform the decision on which one to discard prior to reporting FRC and other lung volumes from a single manoeuvre. Two acceptable FRC manoeuvres not meeting the least stringent repeatability criteria is expected to be an infrequent occurrence—in this case, a specific concern about one manoeuvre may not be present and it is recommended to obtain another manoeuvre to determine which is the outlier.

For body plethysmography, if two grade A manoeuvres meeting the best repeatability are not obtained, the report should include a caution to the interpreter that testing was suboptimal (see standardised operator comments in Supplement). For MBW and helium dilution, only one manoeuvre may be feasible in clinical practice, and this can be reported if acceptable or useable with a note of caution that repeatability could not be assessed. Based on common practice for MBW and the challenge in obtaining acceptable manoeuvres, the mean of all acceptable and useable tests within 25% repeatability can be reported for MBW and helium dilution as an alternative to the preference for two or more acceptable and repeatable maneuvers noted above.

Report format
Laboratories should follow ATS recommendations for reporting of lung volume measurements with specific additions as noted for specific methods in this document [27]. To achieve interoperability, all pulmonary function devices should have the capability to export standardised pulmonary function test data to electronic medical records [43]. Testing session data file requirements have been listed in D1CO and spirometry technical standards [10, 18], additional values specific to lung volume measurement are listed in the Supplement. Operator comments are a key part of the report (see Supplement). The operator should give comments on the test session and must report any quality issues (see acceptability Tables). Comparison with prior values during interpretation is important. Therefore, reports should always include trends.

REFERENCE VALUES

The Global Lung Function Initiative (GLI) reference set provides contemporary sex specific reference values for TLC and its subdivisions across the age range 5-80 years using data from 11 countries [44]. Currently, the GLI reference values have data only from subjects of European ancestry. There are few published studies of non-European reference values [45]. Due to many concerns with the use of race and ethnicity as a biological variable including their inconsistent definitions, marked heterogeneity within these groups, and the risk of contributing to health inequities by normalizing differential exposure to social and environmental influences on lung function, race-specific equations are not recommended [46]. However, because multi-racial reference equations for lung volumes are not available, we recommend use of the Global Lung Function Initiative (GLI) reference equations on an interim basis. The GLI reference equations can be utilised for plethysmographic, washout, and dilution test methodologies. Caution is recommended when using GLI reference equations for those of non-European ancestry. For communities where most people are not represented by the GLI reference equations, reference equations meeting rigorous quality standards [47, 48] and that represent an average inclusive of the diversity of the local population may be appropriate. Laboratories should ensure that local measurement techniques match those used to generate data used for derivation of reference equations. The taskforce is currently unable to recommend reference equations for imaging methodologies.

FUTURE DIRECTIONS AND KEY RESEARCH QUESTIONS

Lung volumes are less repeatable than FEV1 or FVC from spirometry. Improved repeatability would increase the value of individual and serial lung volume measurements. TLC and RV are derived from FRC and linked spirometry which each have measurement errors that may add together and contribute to the larger variability compared to FEV1 and FVC. Analysis of the sources of variability and efforts to reduce the variability of both FRC and linked spirometry can improve repeatability of lung volume measurements. Other techniques such as imaging have different sources of variability and thus there is potential for higher repeatability compared to traditional methods through better characterisation and implementation. The clinical utility of lung volume measurements will be enhanced by having reference data available from
populations that are the same or similar to those used for spirometry. Such data can contribute to interpretation of physiologic patterns that suggest disease categories by making results concordant between spirometry and lung volumes. The diversity of populations contributing to reference data for both lung volumes and other pulmonary function tests must be increased. The acceptability and grading criteria presented in this document should be evaluated for achievability and performance in yielding accurate and precise results. An understanding of the relationship between acceptability and the likelihood of repeatability is needed. Availability and monetary and environmental costs of helium make the sustainability of the helium dilution technique uncertain.
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<td>• Measures all thoracic gas</td>
<td>• Potential for claustrophobia</td>
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<td>• Requires only short time to repeat measurements</td>
<td>• Can overestimate FRC in severe obstruction</td>
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<td>• Stable end-tidal lung volume*</td>
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<td>• Overlapping straight lines with no thermal drift</td>
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<td>• Pant frequency 0.5-1 Hz OR</td>
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<td>Pant freq &gt; 1.0-1.5 Hz with no or minimal obstruction on spirometry</td>
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<td><strong>Pre-shutter closure:</strong></td>
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<td>• Unstable end-tidal lung volume* without significant shift in either direction</td>
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<td>• Portions of overlapping straight lines</td>
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<td>• Unstable end tidal lung volume* with significant shift in either direction (e.g., increase in end expiratory lung volume with each breath)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>During shutter closure:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Open pants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No straight lines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Excessive thermal drift</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pants are clipped (mouth pressure transducer range exceeded)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pant frequency &lt; 0.5 Hz, &gt; 2.0 Hz, or &gt; 1.5 Hz and evidence of significant obstruction on spirometry</td>
<td></td>
</tr>
</tbody>
</table>

Useable – interpret with caution.
See Supplemental Figures 1-3 for examples of normal and abnormal tracings.
* stability defined as ≥ 3 tidal breaths with the difference between maximum and minimum end-expiratory lung volume within 15% of the tidal volume [10].

* stability defined as ≥ 3 tidal breaths with the difference between maximum and minimum end-expiratory lung volume within 15% of the tidal volume [10].
<table>
<thead>
<tr>
<th>Classification</th>
<th>Acceptability and Grading Criteria for FRC Measurement by Multiple Breath Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptable</strong></td>
<td><strong>Tidal breathing prior to washout and washout phase characteristics</strong></td>
</tr>
<tr>
<td></td>
<td>Pre-switch-in:</td>
</tr>
<tr>
<td></td>
<td>• Relaxed tidal breathing with stable end-tidal lung volume*</td>
</tr>
<tr>
<td></td>
<td>During washout:</td>
</tr>
<tr>
<td></td>
<td>• Relaxed tidal breathing without sigh, cough, or breath-hold</td>
</tr>
<tr>
<td></td>
<td>• Flow is stable with no forced breathing or signs of hyperventilation (CO₂ within 4-6% range if available)</td>
</tr>
<tr>
<td></td>
<td>• No evidence of leak</td>
</tr>
<tr>
<td></td>
<td>• End of test criteria met (three consecutive tidal breaths under target concentration)</td>
</tr>
<tr>
<td></td>
<td>When performed:</td>
</tr>
<tr>
<td></td>
<td>• Adequate wait time between MBW manoeuvres (≥ twice the washout time; longer with obstructive lung disease)</td>
</tr>
<tr>
<td><strong>Useable</strong></td>
<td><strong>As for acceptable except any of:</strong></td>
</tr>
<tr>
<td></td>
<td>Pre-switch-in:</td>
</tr>
<tr>
<td></td>
<td>• Unstable end-tidal lung volume* without significant shift in either direction</td>
</tr>
<tr>
<td></td>
<td>• Irregular tidal breaths (swallow, small breath) in pre-phase</td>
</tr>
<tr>
<td></td>
<td>During washout:</td>
</tr>
<tr>
<td></td>
<td>• Irregular first breath of washout (swallow, small breath)</td>
</tr>
<tr>
<td></td>
<td>• Sigh, cough, or breath-hold in rest of washout but no increase in end-tidal tracer gas concentration</td>
</tr>
<tr>
<td></td>
<td>• End-tidal lung volume is unstable during washout but no increase in end-tidal tracer gas concentration</td>
</tr>
<tr>
<td><strong>Not acceptable or useable (reject)</strong></td>
<td><strong>Any of:</strong></td>
</tr>
<tr>
<td></td>
<td>Pre-switch-in:</td>
</tr>
<tr>
<td></td>
<td>• Unstable end tidal lung volume* with significant shift in either direction (e.g., increase in end expiratory lung volume with each breath)</td>
</tr>
<tr>
<td></td>
<td>• Flow is highly erratic with or without forced breathing or hyperventilation (CO₂ outside 4-6% range if available)</td>
</tr>
<tr>
<td></td>
<td>• Sigh, cough, or breath-hold</td>
</tr>
<tr>
<td></td>
<td>During washout:</td>
</tr>
<tr>
<td></td>
<td>• Sigh, cough, or breath-hold in first breath of washout</td>
</tr>
<tr>
<td></td>
<td>• Sigh, cough, or breath-hold in rest of washout resulting in increase in end-tidal tracer gas concentration†</td>
</tr>
<tr>
<td></td>
<td>• Significant shifts in end-tidal lung volume during washout resulting in increase in end-tidal tracer gas concentration†</td>
</tr>
<tr>
<td></td>
<td>• Flow is highly erratic with or without forced breathing or hyperventilation (CO₂ outside 4-6% range if available)</td>
</tr>
<tr>
<td></td>
<td>• Evidence of leak</td>
</tr>
<tr>
<td></td>
<td>• End of test criteria not met: manoeuvre does not have three consecutive tidal breaths under target concentration</td>
</tr>
<tr>
<td>When performed:</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>• Inadequate wait time between MBW manoeuvres for gas concentrations to re-equilibrate (less than twice the washout time or end-tidal tracer gas concentration has not returned to baseline)</td>
<td></td>
</tr>
</tbody>
</table>

Pre-switch-in (also known as pre-phase) – grading criteria are relevant to the last three breaths before the washout phase.

During washout – grading criteria are relevant to all breaths of the washout until the end of test criteria is reached.

Acceptable manoeuvres can be challenging to obtain in MBW, especially in young children. Useable – interpret with caution.

See Supplemental Figures 3-4 for examples of normal and abnormal tracings.

* stability defined as ≥ 3 tidal breaths with the difference between maximum and minimum end-expiratory lung volume within 15% of the tidal volume [10].

† Increases in end-tidal tracer gas concentration during the washout in response to irregular breathing pattern can indicate the release of trapped gas from unventilated regions of the lung and is a reason to reject the trial.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Acceptability and Grading Criteria for FRC Measurement by Helium Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptable</strong></td>
<td><em>Tidal breathing prior to dilution phase and dilution phase characteristics</em></td>
</tr>
<tr>
<td>Pre-switch-in:</td>
<td>• Stable end-tidal lung volume*</td>
</tr>
<tr>
<td>During dilution:</td>
<td>• Relaxed tidal breathing without sigh, cough, or breath-hold</td>
</tr>
<tr>
<td></td>
<td>• Stable end-tidal lung volume</td>
</tr>
<tr>
<td></td>
<td>• No leak</td>
</tr>
<tr>
<td></td>
<td>• End of test criteria met: ($\Delta[\text{He}] &lt; 0.02% \times 30\text{ sec.}$)</td>
</tr>
<tr>
<td>When performed:</td>
<td>• Adequate wait time between manoeuvres ($\geq$ twice the dilution time; longer with obstructive lung disease)</td>
</tr>
<tr>
<td><strong>Useable</strong></td>
<td><strong>As for acceptable except any of:</strong></td>
</tr>
<tr>
<td>Pre-switch-in:</td>
<td>• Unstable end-tidal lung volume* without significant shift in either direction</td>
</tr>
<tr>
<td>During dilution:</td>
<td>• Non-uniform dilution curve</td>
</tr>
<tr>
<td></td>
<td>• Minimally unstable end-tidal lung volume</td>
</tr>
<tr>
<td></td>
<td>• Sigh, cough, or breath-hold with no leak</td>
</tr>
<tr>
<td><strong>Not acceptable or useable (reject)</strong></td>
<td><strong>Any of:</strong></td>
</tr>
<tr>
<td>Pre-switch-in:</td>
<td>• Unstable end tidal lung volume* with significant shift in either direction (e.g., increase in end expiratory lung volume with each breath)</td>
</tr>
<tr>
<td>During dilution:</td>
<td>• Unacceptable breathing pattern</td>
</tr>
<tr>
<td></td>
<td>• Evidence of leak</td>
</tr>
<tr>
<td></td>
<td>• Failed end of test</td>
</tr>
<tr>
<td>When performed:</td>
<td>• Inadequate wait time between manoeuvres</td>
</tr>
</tbody>
</table>

Useable – interpret with caution.

* stability defined as $\geq 3$ tidal breaths with the difference between maximum and minimum end-expiratory lung volume within 15% of the tidal volume [10].
<table>
<thead>
<tr>
<th>Classification</th>
<th>Spirometry manoeuvre after FRC measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable*</td>
<td>• Linked spirometry</td>
</tr>
<tr>
<td></td>
<td>• SVC is greater than FVC or</td>
</tr>
<tr>
<td></td>
<td>If &gt; 6 yr, SVC is up to 150 mL less than FVC</td>
</tr>
<tr>
<td></td>
<td>If ≤ 6 yr, SVC is up to 100 mL less than FVC or 10% of FVC, whichever is greater</td>
</tr>
<tr>
<td>Useable*</td>
<td>Any of:</td>
</tr>
<tr>
<td></td>
<td>• Unlinked spirometry with an MBW or helium dilution FRC measurement with stable pre-phase end-tidal lung volume†</td>
</tr>
<tr>
<td></td>
<td>• If &gt; 6 yr, SVC is between 150-250 mL less than FVC</td>
</tr>
<tr>
<td></td>
<td>• If ≤ 6 yr, SVC is between 100-200 mL less than FVC, or 10% of FVC, whichever is greater</td>
</tr>
<tr>
<td>Not acceptable or useable (reject)</td>
<td>Any of:</td>
</tr>
<tr>
<td></td>
<td>• Unlinked spirometry in body plethysmography</td>
</tr>
<tr>
<td></td>
<td>• Unlinked spirometry with an MBW or helium dilution FRC measurement with unstable pre-phase end-tidal lung volume†</td>
</tr>
<tr>
<td></td>
<td>• If &gt; 6 yr, SVC is &gt; 250 mL less than FVC</td>
</tr>
<tr>
<td></td>
<td>• If ≤ 6 yr, SVC is &gt; 200 mL less than FVC, or 10% of FVC, whichever is greater</td>
</tr>
</tbody>
</table>

Useable – interpret with caution.

*Meets ATS/ERS acceptability criteria for within-manoeuvre evaluation of IC and SVC [10].

If forced spirometry is not performed in the same session with lung volumes, an alternative is to require that at least three measures of VC that meet ATS/ERS acceptability criteria for within-manoeuvre evaluation are obtained and that the largest and next largest of these VC satisfy the stated ranges for the comparison of SVC to FVC.

† stability defined as ≥ 3 tidal breaths with the difference between maximum and minimum end-expiratory lung volume within 15% of the tidal volume [10].
Table 6: Grading System for a Lung Volume Test Performed by Body Plethysmography

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of FRC† measurements</th>
<th>Number of SVC measurements</th>
<th>Repeatability* of FRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≥ 3 acceptable</td>
<td>≥ 3 acceptable</td>
<td>Within 5%</td>
</tr>
<tr>
<td>B</td>
<td>≥ 2 acceptable</td>
<td>≥ 2 acceptable</td>
<td>Within 5%</td>
</tr>
<tr>
<td>C</td>
<td>≥ 2 acceptable</td>
<td>≥ 2 acceptable</td>
<td>Within 10%</td>
</tr>
<tr>
<td>D</td>
<td>≥ 1 acceptable AND ≥ 1 useable</td>
<td>≥ 1 acceptable AND ≥ 1 useable</td>
<td>Within 10%</td>
</tr>
<tr>
<td>E</td>
<td>1 acceptable AND 0 useable</td>
<td>1 acceptable AND 0 useable</td>
<td>N/A</td>
</tr>
<tr>
<td>U</td>
<td>0 acceptable AND ≥ 1 useable</td>
<td>0 acceptable AND ≥ 1 useable</td>
<td>Within 10%</td>
</tr>
<tr>
<td>F</td>
<td>0 acceptable or useable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall grade is lowest of FRC, SVC and FRC repeatability grades. For example, if number of FRC measurements and repeatability of FRC are both grade A (3 acceptable efforts and repeatable), but SVC is grade B (only 2 acceptable efforts) – then overall grade is B.

The number of measurements refer to the manoeuvres used for calculation of FRC and other lung volumes.

† if all spirometry manoeuvres are not acceptable or usable, report FRC only.

* difference between the highest and lowest value divided by the mean x 100.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of FRC† measurements</th>
<th>Number of SVC measurements</th>
<th>Repeatability* of FRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≥ 2 acceptable</td>
<td>≥ 2 acceptable</td>
<td>Within 10%</td>
</tr>
<tr>
<td>B</td>
<td>1 acceptable AND ≥ 1 useable</td>
<td>1 acceptable AND ≥ 1 useable</td>
<td>Within 10%</td>
</tr>
<tr>
<td>C</td>
<td>≥ 2 useable</td>
<td>≥ 2 useable</td>
<td>Within 10%</td>
</tr>
<tr>
<td>D</td>
<td>≥ 2 acceptable OR useable</td>
<td>≥ 2 useable</td>
<td>Within 25%</td>
</tr>
<tr>
<td>E</td>
<td>1 acceptable AND 0 useable</td>
<td>1 acceptable AND 0 useable</td>
<td>N/A</td>
</tr>
<tr>
<td>U</td>
<td>0 acceptable AND 1 useable</td>
<td>0 acceptable AND 1 useable</td>
<td>N/A</td>
</tr>
<tr>
<td>F</td>
<td>0 acceptable or useable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall grade is lowest of FRC, SVC and FRC repeatability grades. For example, if number of FRC measurements and repeatability of FRC are both grade A (2 acceptable efforts and repeatable), but SVC is grade B (1 acceptable AND 1 useable) – then overall grade is B.

The number of measurements refer to the manoeuvres used for calculation of FRC and other lung volumes.

† if all spirometry manoeuvres are not acceptable or useable, report FRC only.

* difference between the highest and lowest value divided by the mean x 100.
References


Figure 1: Static lung volumes and capacities based on a volume–time spirogram of an expiratory vital capacity. IRV: inspiratory reserve volume; $V_T$: tidal volume; ERV: expiratory reserve volume; RV: residual volume; IC: inspiratory capacity; FRC: functional residual capacity; TLC: total lung capacity.
Figure 2: Volume–time display showing the sequence of quiet breathing and, after stable end-expiratory level is achieved, a short period when the shutter is closed for determination of the thoracic gas volume, followed by an open-shutter period during which the patient stays on the mouthpiece and performs an inspiratory capacity (IC) manoeuvre followed by a slow expiratory vital capacity manoeuvre. In a linked manoeuvre, all volumes are determined without the patient coming off the mouthpiece. FRC: functional residual capacity; IRV: inspiratory reserve volume; \( V_T \): tidal volume; RV: residual volume; ERV: expiratory reserve volume; TLC: total lung capacity.
Figure 3: In a healthy patient, expiratory vital capacity manoeuvres performed in a forced (FVC) or slow (SVC) manner are expected to yield the same result. However, in a patient with an obstructive ventilatory defect, there is potential for dynamic gas trapping and overestimation of RV with a forced manoeuvre.
Figure 4: Display of a properly performed panting manoeuvre as a series of almost superimposed straight lines separated by only a small thermal drift. The target panting frequency is between 0.5 and 1 Hz.
Figure 5: Display of the time course of Nitrogen (%) and Flow (L/s) throughout the standard multiple breath washout measurement with the patient breathing 100% O₂. When expressed as N₂% vs volume instead of time (not shown), the area under the curve would be the N₂ volume washed out.
Figure 6: Helium dilution setup utilizing a volume displacement spirometry. The spirometric tracing will have a rising baseline as show in red if CO₂ absorption and O₂ consumption are not accounted for by continuous addition of an appropriate amount of O₂. Reproduced from Hughes ‘Physiology and Practice of Pulmonary function’, published by Association for Respiratory Technology & Physiology (permission granted).
Figure 7: Helium dilution setup utilizing a pneumotachometer and rebreathing bag. Volumes of 100% oxygen are added to the bag to compensate for oxygen consumption to keep the oxygen percentage in the circuit and the circuit volume constant. Helium is analyzed by continuously sampling gas that is pumped from the rebreathing bag.
Figure 8: Display of an acceptable profile for a helium dilution test to determine functional residual capacity (FRC), in which O₂ is continually added to compensate for O₂ consumption. Once equilibration is reached, a patient is switched from breathing helium to room air. FHe1: helium fraction at the time that the patient is connected to the apparatus (10.9% in this example); IC: inspiratory capacity; IRV: inspiratory reserve volume; Vₜ: tidal volume; RV: residual volume; ERV: expiratory reserve volume.
Supplemental material for:


Authors:

**ONLINE SUPPLEMENTAL MATERIAL**

Supplementary information about literature research
- Search Terms Tables: Techniques, Reference values, Imaging
- Results by Search
- PRISMA Flow Diagram

Best practices for accurately measuring standing height
Data file requirements and standardised operator comments
Measurement of lung volume using Imaging techniques
- Patient coaching and cooperation
- Conventional radiographs
- Computed tomography (CT)
- Magnetic resonance imaging
- Controversies and critical questions

New technologies
- Minibox
- Optoelectronic plethysmography (OEP)
- Inspired sine-wave technique (IST)
- Single breath oxygen dilution

PFT System validation/verification

Supplemental figures to aid in grading manoeuvres

Airway resistance measured by body plethysmography
- Background
- Measurement technique
- Special considerations in children
- Equipment
- Measurement
- Quality control
- Raw outcomes
- Methods to calculate slope values
- Reference values for airway resistance from body plethysmography

**SUPPLEMENTARY INFORMATION ABOUT LITERATURE SEARCH INCLUDING PRISMA FLOW DIAGRAM**
Tables 1-4 list search terms. A search for sulfur hexafluoride was performed separately because it was not included in the initial TECHNIQUES search strategy.

Note for Embase: search limited to words in the title or author-supplied keywords

Search terms tables:

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp lung volume measurements/ or total lung capacity/ or functional residual capacity/ or residual volume/ [Medline]</td>
</tr>
<tr>
<td>2</td>
<td>((pulmonary or lung$ or ventilatory or respiratory or residual) adj2 (capacit$ or volume$)).ti,ab,kw. [text words for the main LV concepts]</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2 [Medline tw or MeSH main LV concept]</td>
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<tr>
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<tr>
<td>6</td>
<td>limit 4 to abstracts</td>
</tr>
<tr>
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<td>8</td>
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<tr>
<td>11</td>
<td>8 or 10 [MAIN LV concept Medline or tw with limits]</td>
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<td>12</td>
<td>nitrogen washout/</td>
</tr>
<tr>
<td>13</td>
<td>((lung$ or nitrogen) adj2 washout$).ti,ab,kw.</td>
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<tr>
<td>14</td>
<td>12 or 13</td>
</tr>
<tr>
<td>15</td>
<td>plethysmography/ or photoplethysmography/ or plethysmography, impedance/ or cardiography, impedance/ or plethysmography, whole body/ [Medline]</td>
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<td>16</td>
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<td>17</td>
<td>15 or 16 [plethysmography Medline]</td>
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<td>18</td>
<td>(helium adj2 (dilution or analy?er$)).ti,ab,kw.</td>
</tr>
<tr>
<td>19</td>
<td>15 or 16 or 18 [Techniques Medline]</td>
</tr>
<tr>
<td>20</td>
<td>14 or 15 or 16 or 18 [Techniques Medline]</td>
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<td>21</td>
<td>11 and 20 [LV and techniques]</td>
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### Table 2: Search terms for REFERENCE VALUES

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<td>exp lung volume measurements/ or total lung capacity/ or functional residual capacity/ or residual volume/ [Medline]</td>
</tr>
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<td>2</td>
<td>((pulmonary or lung$ or ventilatory or respiratory or residual) adj2 (capacit$ or volume$)).ti,ab,kw. [text words for the main LV concepts]</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2 [Medline tw or MeSH main LV concept]</td>
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<tr>
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<td>limit 3 to yr=&quot;2004 -Current&quot;</td>
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<td>9</td>
<td>limit 7 to animals</td>
</tr>
<tr>
<td>10</td>
<td>7 not 8 not 9</td>
</tr>
<tr>
<td>11</td>
<td>8 or 10 [MAIN LV concept Medline or tw with limits]</td>
</tr>
<tr>
<td>12</td>
<td>Reference Values/ [Medline]</td>
</tr>
<tr>
<td>13</td>
<td>((normal adj (range$ or value$)) or ((reference or predictive or control) adj (range$ or value$ or interval$ or equation$))).ti,ab,kw.</td>
</tr>
<tr>
<td>14</td>
<td>12 or 13</td>
</tr>
<tr>
<td>15</td>
<td>11 and 14 [LV and ref values]</td>
</tr>
</tbody>
</table>

### Table 3: Search terms for IMAGING

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<th>Searches</th>
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<tbody>
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<td>exp lung volume measurements/ or total lung capacity/ or functional residual capacity/ or residual volume/ [Medline]</td>
</tr>
<tr>
<td>2</td>
<td>((pulmonary or lung$ or ventilatory or respiratory or residual) adj2 (capacit$ or volume$)).ti,ab,kw. [text words for the main LV concepts]</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2 [Medline tw or MeSH main LV concept]</td>
</tr>
<tr>
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<td>limit 3 to yr=&quot;2004 -Current&quot;</td>
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<td>limit 4 to English language</td>
</tr>
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<td>limit 4 to abstracts</td>
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<td>limit 7 to humans</td>
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<td>7 not 8 not 9</td>
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<td>11</td>
<td>8 or 10 [MAIN LV concept Medline or tw with limits]</td>
</tr>
<tr>
<td>12</td>
<td>Ultrasonography, Doppler/ [Medline]</td>
</tr>
</tbody>
</table>
Ultrasonography/ [Medline]
(ultrasound or phonophores$ or ultrasonograph$ or ultrasonic$ or sonication or sonification).ti,ab,kw.
12 or 13 or 14 [ultrasound Medline]
radiography, thoracic/ or bronchography/ or mass chest x-ray/
((thorax or thoracic or chest or lung$) adj2 (x-ray$ or radiogra$ or radiolog$ or roentgeno$)).ti,ab,kw.
16 or 17 [chest radiograph Medline]
tomography/ or tomography, x-ray computed/ or four-dimensional computed tomography/ or tomography, spiral computed/ or multidetector computed tomography/ [CT Medline]
((computer$ adj2 (assisted or diagnos$)) or CAT scan$ or (compute$ adj3 tomograph$) or tomoscintigra$ or CT scan$ or PET).ti,ab,kw.
19 or 20
magnetic resonance imaging/ or diffusion magnetic resonance imaging/ or diffusion tensor imaging/ or echo-planar imaging/ or fluorine-19 magnetic resonance imaging/ or multiparametric magnetic resonance imaging/ [Medline]
(MRI or MRIs or (magneti$ adj2 resonance adj2 imag$)).ti,ab,kw.
22 or 23
11 and 15 [LV and ultrasound]
11 and 18 [LV and radiograph]
11 and 21 [LV and CT]
11 and 24 [LV and MRI]
or/25-28 [LV and all imaging]

Table 4: SULFUR HEXAFLUORIDE
Ovid MEDLINE and In-Process, In-Data-Review & Other Non-Indexed Citations

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp lung volume measurements/ or total lung capacity/ or functional residual capacity/ or residual volume/ [Medline]</td>
</tr>
<tr>
<td>2</td>
<td>((pulmonary or lung$ or ventilatory or respiratory or residual) adj2 (capacit$ or volume$)).ti,ab,kw. [text words for the main LV concepts]</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2 [Medline tw or MeSH main LV concept]</td>
</tr>
<tr>
<td>4</td>
<td>limit 3 to yr=&quot;2004 -Current&quot;</td>
</tr>
<tr>
<td>5</td>
<td>limit 4 to English language</td>
</tr>
<tr>
<td>6</td>
<td>limit 4 to abstracts</td>
</tr>
<tr>
<td>7</td>
<td>5 or 6</td>
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<td>8</td>
<td>limit 7 to humans</td>
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<td>9</td>
<td>limit 7 to animals</td>
</tr>
<tr>
<td>10</td>
<td>7 not 8 not 9</td>
</tr>
</tbody>
</table>
Results by search:

All techniques: 2660 abstracts reviewed (includes some duplicates), 110 selected abstracts, 109 full-text articles retrieved (excluded ones that were not in English or not available) and reviewed.

Reference Values: 1659 abstracts reviewed (includes some duplicates), 43 selected abstracts, 37 full-text articles retrieved and reviewed.

Imaging: 5460 abstracts reviewed (includes some duplicates), 131 selected abstracts, 123 full-text articles retrieved and reviewed.

There were a small number of duplicates between the above three search groups leading up to review of full-text articles.

A reason was not recorded for all abstracts excluded. In all cases, the goal was to exclude abstracts of studies not providing information on technical performance of lung volumes or that were about tests not performed volitionally by adults or children.
Records identified through database searching
(n = 2,660 for All Techniques
n = 1,659 for Reference Values
n = 5,460 for Imaging)

Additional records identified through other sources
(n = 30)

Records including a few duplicates
(n = 9,809)

Records screened
(n = 9,809)

Records excluded (see below for reasons)
(n = 9,510)

Full-text articles assessed for eligibility
(n = 299)

Studies included in qualitative synthesis
(n = 107)

Studies included in quantitative synthesis
(meta-analysis)
(N/A)

Full-text articles excluded
(n = 192)

Reasons for exclusion:

a. Majority: Not related to technical performance (“how-to”) or comparison of methods, only clinical interpretation
b. Tests not performed volitionally by adults or children (e.g. infants)
c. Not in English
d. FRC measurements during mechanical ventilation
BEST PRACTICES FOR ACCURATELY MEASURING STANDING HEIGHT

- For height measurement in adults and children > 2 years, standing height is measured with a wall mounted stadiometer.
- Ensure the stadiometer is checked and validated.
- Ensure the stadiometer is wiped clean before use.
- Measure height without shoes.
- Remove headwear that interferes with the measurement.
- If the headwear cannot be adjusted (for instance due to religious reasons), measure total height including the headwear, and then measure the height of the headwear. Subtract height of the headwear from total height to obtain the height measurement. Make a note of this deviation from the standard measurement in the report.
- Ensure the individual is standing upright, as tall and straight as possible, heels against the wall, feet slightly apart, looking straight ahead with the head in the so-called Frankfort plane (see Figure). This is achieved when the lower border of the eye socket is in a horizontal line with the middle of the ear hole.
- Record height to the nearest 0.1 cm.

Frankfort plane:

DATA FILE REQUIREMENTS and STANDARDISED OPERATOR COMMENTS

Standardised data must be available for the testing session and include all manoeuvres within the session (Table 5). Some laboratories may choose not to report all available parameters. Empty fields or missing values should be marked as “null”. Note that the next section provides details of the standardised operator comments. All volumes are reported in liters BTPS (except for those specified as milliliters BTPS).

Table 5: Data file requirements

<table>
<thead>
<tr>
<th>Patient information</th>
<th>(as in Section E10: Spirometry testing session data file requirements, 2019)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab information</td>
<td>(as in Section E10: Spirometry testing session data file requirements, 2019)</td>
</tr>
<tr>
<td>Bronchodilator information</td>
<td>(as in Section E10: Spirometry testing session data file requirements, 2019)</td>
</tr>
<tr>
<td>Data for each manoeuvre</td>
<td></td>
</tr>
<tr>
<td>- Test type (pre- or post- bronchodilator)</td>
<td></td>
</tr>
<tr>
<td>- Time of start of manoeuvre (HH:MM)</td>
<td></td>
</tr>
<tr>
<td>- TLC</td>
<td></td>
</tr>
<tr>
<td>- VC</td>
<td></td>
</tr>
<tr>
<td>- IC</td>
<td></td>
</tr>
<tr>
<td>- FRC</td>
<td></td>
</tr>
<tr>
<td>- ERV</td>
<td></td>
</tr>
<tr>
<td>- RV</td>
<td></td>
</tr>
<tr>
<td>- Grade</td>
<td></td>
</tr>
<tr>
<td>- Operator comments</td>
<td></td>
</tr>
</tbody>
</table>

Values reported for the full lung volumes session (for all 3 methods):

- Reference values source (e.g. GLI-2012)
- Measured value, LLN, ULN, z-score and percent of predicted must be provided for the following parameters:
  - TLC
  - VC
  - IC
  - FRC
  - ERV
  - RV
  - RV/TLC
  - Post-bronchodilator values for above if performed
  - Operator comments relating to quality of testing session

Additional data for Body plethysmography manoeuvres

- Panting frequency
- VTG
- Airway resistance data
  - Raw
  - SGaw
  - VTG associated with the airway resistance manoeuvre
Panting frequency

Additional data for MBW manoeuvres
- Washout time
- Tracer gas concentration at start and end of test
- Cumulative expired volume
- Lung clearance index at 2.5%

Additional data for Helium dilution manoeuvres
- Equilibration time
- He fraction at the beginning and at the end of test
- Spirometry apparatus volume if applicable

Standardised operator comments

The use of standardised operator comments is strongly encouraged to promote standardised reporting and to meaningfully guide interpretation. The system should allow the facility manager to edit the list of comments and add items specific to a given facility or application.

- Report grade of testing with number of manoeuvres used and degree of repeatability. Example: Grade A, two acceptable maneuvers with FRC within 5%.
- Technical criteria that manoeuvres did not met when testing is not grade A.
- Suboptimal results were obtained. Results should be interpreted with caution.
- Only one acceptable or usable manoeuvre obtained for MBW (or He dilution). Repeatability could not be assessed. Results should be interpreted with caution.
- Patient was too tired to continue
- Coordination difficulties
- Patient claustrophobic – measurement not attempted (for plethysmography)
- Other [prompt for description]
MEASUREMENT OF LUNG VOLUME USING IMAGING TECHNIQUES

Patient coaching and cooperation
As with the other techniques described to measure total lung volume via imaging, patients must be coached to achieve maximal inspiration. In research studies, spirometric gating has not consistently yielded higher total lung capacities [1-4] and the use of an occlusion shutter to hold lung volume is uncommon. When the goal is to make measurements only at maximal inflation, patients do not have to achieve a stable FRC, stay on a mouthpiece, or exhale fully.

Conventional radiographs
The principle is to outline the lungs in both anteroposterior and lateral chest radiographs and determine the outlined areas either by assuming a given geometry or by using planimeters in order to derive the confined volume. Adjustments are made for magnification factors, volumes of the heart, the intrathoracic tissue and blood, and infradiaphragmatic spaces. Analysis of chest radiographs to obtain lung volumes in children and adults has been reviewed in more detail in a previous report [5]. In the determination of TLC, the difference between plethysmographic and radiographic measurements exceeded 20% in some studies. The difference was found to be greater in paediatric populations for unknown reasons.

Computed tomography (CT)
In addition to thoracic cage volumes, CT can provide estimates of lung tissue and air volumes, and can also estimate the volume of lung occupied by increased density (e.g. in patchy opacities) or decreased density (e.g. in emphysema or bullae). In the setting of severe airflow obstruction where physiologic techniques under- or over-estimate lung volumes, imaging studies have the potential to provide unique information. CT measurements slightly underestimate TLC by roughly 6% in individuals without a ventilatory defect [6, 7] and by more than 20% in those with COPD [8-10] compared with plethysmography, with $r^2$ ranging from 0.59-0.92 [4, 8]. The varying results across studies may reflect differences in the image analysis used to isolate lung, tissue, and air volumes. Different software packages and reconstruction algorithms have little effect on estimates of TLC [6, 11]. In one study, compared to the supine position, CT scans performed in the sitting or standing position led to 12% higher values and much better agreement with plethysmographic TLC [12]. The study finding the best agreement for TLC between CT and plethysmography used spirometric gating [2]. TLC estimates from CT scans have longitudinal reproducibility comparable to other methods [11, 13-15]; however, one study found a higher intra-individual variation of 16% [16]. CT measurements of TLC correlate and agree better with plethysmography than do CT measurements of RV [6, 14, 17]. In clinical practice, streak artifacts from overlying or implanted metal hardware, pneumonectomy, and abdominal gas can lead to failure of the analysis or erroneous results [18]. A disadvantage of using CT is the higher radiation dose compared to conventional radiography. The dose can be considerably diminished without affecting lung volume measurement [19]. Reference values for CT-based lung volumes have been published [20-24].

Magnetic resonance imaging
Magnetic resonance imaging (MRI) offers the advantage of a large number of images within a short period of time, so that volumes can be measured within a single breath. As with CT, MRI offers the potential for scanning specific regions of the lung, as well as the ability to adjust for lung water and tissue. However, despite the advantages of an absence of radiation exposure, the use of MRI for measuring thoracic gas volume will be limited by its considerable cost, limited availability, measurements not done in the upright position, and limited data suggesting even less accuracy and correlation than CT imaging [25].

**Controversies and critical questions**

There is inadequate data in the literature to support recommending one specific technique over the other, or to standardise imaging techniques for measurement of thoracic gas volumes. It is a question of whether TLC values obtained from chest imaging are sufficiently close to those achieved in pulmonary function laboratories. In patients with lung disease, the difference between radiographic measurements and lung function measurements may be due to differences in the ability to exclude tissue without airspace, leading to a tendency for the radiographic method to give higher values.
NEW TECHNOLOGIES

While this document focuses on measuring lung volumes by body plethysmography, nitrogen washout, helium dilution and imaging, it is worth noting that there are other methods to measure lung volumes as well.

**Minibox™**
The Minibox™ is a commercial device that measures lung volumes by analysis of gas pressures and flows immediately preceding and following airway occlusion during tidal breathing [26]. By applying the principle of Boyle’s Law, the Minibox™ calculates TLC from a mathematical model whose parameters are inferred from empirical data derived from body plethysmography. The device is compact and portable and has been found to produce measurements of lung volumes that are comparable to those measured directly using body plethysmography in small groups of healthy people and those with restrictive and obstructive lung disease. Further validation in larger groups of people with and without lung disease is needed.

**Optoelectronic plethysmography (OEP)**
OEP is a method to assess lung volumes based on 3-dimensional optical displacement of markers placed on the chest wall [27]. It is a unique method that does not require breathing into a device and in which the measurements are not influenced by environmental factors of temperature, humidity barometric pressure and gas concentration. OEP allows calculation of the volumes of the three compartments of the chest wall, including pulmonary rib cage, abdominal rib cage and abdomen. From these measurements the tidal volume and end-expiratory lung volume of each compartment is calculated. OEP does not calculate conventional lung volumes such as TLC or FRC directly, and is more suited to analyzing breathing patterns. OEP has been applied in many settings, including asthma, COPD exercise, mechanical ventilation, and neuromuscular disease.

**Inspired sine-wave technique (IST)**
The IST is a method to monitor the concentration of a tracer gas (nitrous oxide) as it is sinusoidally modulated in inspired air during tidal breathing [28]. Modulation of amplitude and phase of the expired sine wave occurs based on pulmonary ventilation, blood flow and ventilation heterogeneity. From the measured data, end-expired lung volume, pulmonary blood flow and indices of ventilation heterogeneity can be derived. IST underestimates FRCpleth but this can be improved by normalizing to age [29]. Within session repeatability is comparable to FRCpleth or helium dilution. No studies have yet been published to demonstrate the method’s accuracy in patients with lung disease.

**Single breath oxygen dilution**
The single breath oxygen dilution method measures lung volumes in a manner similar to helium dilution [30]. The method is accurate in measuring TLC and FRC in healthy subjects and is attractive due to portability and lack of need for inert gas. Validation of the technique is needed in patients with lung disease.
PFT SYSTEM VALIDATION/VERIFICATION

Recommended validation/verification process when onboarding a new PFT system or with major software operation upgrades.

1. Perform over a 3-5 day period.
2. Syringe linearity testing
   a. Complete 5 syringe linearity tests on the flow/volume measuring module
      i. Perform three strokes using a calibrated 3L syringe at each flow profile (<2L, 4-6L, >8L).
      ii. Target difference from the highest measured volume to lowest measured volume ≤ 90 ml
3. Isothermal lung volume test
   a. Manufacturers must have isothermal lung analogs of two different sizes compatible with their devices for assessing accuracy of TGV. Ideally, isothermal lung analogs will be provided with the equipment at initial purchase, and for existing users, available for purchase separately.
   b. Complete 3 isothermal lung volume measurements
      i. Within the specifications of the device
4. Biological Control Testing (BioQC)
   a. Biological Subject testing
      i. Perform 10 tests for each affected testing module
      ii. Compare the mean to the previously measured values on the BioQC subject.
      iii. Identify a larger than expected difference in means
         1. Spirometry – <2 standard deviations of the baseline BioQC data (which is often <200 mL or <5%)
         2. FRC or TLC – <2 standard deviations of the baseline BioQC data (which is often ≤ 0.5L or ≤10%)
5. Subject comparison as an alternative to BioQC testing
   a. 10 patients tested on both systems with a range of lung function normality or abnormality (mild, moderate, severe obstruction and restriction.

A Diagnostic Accreditation Program spreadsheet to facilitate QC is available as a supplemental file.
SUPPLEMENTAL FIGURES TO AID IN GRADING MANOEUVRGES

**Supplemental Figure 1:** Examples of normal and abnormal closed shutter plethysmography tracings in the setting of thermal drift.

- **A:** Normal closed shutter manoeuvre with the loop nearly closed.
- **B:** Open loops due to thermal drift.

**Supplemental Figure 2:** Further examples of normal and abnormal closed shutter plethysmography loops.
Supplemental Figure 3: Example when the shutter is not closed at FRC during plethysmography measurement of lung volumes. A short delay in shutter closure leads to a small offset between FRC and VTG (FRC less than VTG). This offset is automatically accounted for by the software for measurement of FRC and other lung volume subdivisions but should be verified by the operator. With or without an offset, the period of shutter closure is followed by an open-shutter period during which the patient stays on the mouthpiece and performs an inspiratory capacity (IC) manoeuvre followed by a slow expiratory vital capacity manoeuvre. In a linked manoeuvre, all volumes are determined without the patient coming off the mouthpiece. FRC: functional residual capacity; IRV: inspiratory reserve volume; $V_T$: tidal volume; RV: residual volume; ERV: expiratory reserve volume; TLC: total lung capacity.
Supplemental Figure 4: Examples of characteristics of acceptable and usable MBW tests on the % Nitrogen, Flow (L/s), and Volume (L) versus Time (s) traces. (continued on next page).
Usable: Adequate wait time between trials. Some irregular breaths (swallow, small breath) in pre-phase or first breath of washout. Sigh, cough, or breath-hold in rest of washout but no in increase in end-tidal tracer gas concentration. EELV is unstable but no increase in end-tidal tracer gas concentration. Flow is moderately variable in pre-phase and washout with no forced breathing or signs of hyperventilation (CO2 within 4-6% range). No evidence of leak. End of test criteria met (three tidal breaths under the target concentration).

Not acceptable or usable due to breathing pattern: Adequate wait time between trials. Sigh, cough, or breath-hold in last breath of pre-phase or first breath of washout. Sigh, cough, or breath-hold in rest of washout resulting in increase in end-tidal tracer gas concentration. Significant instability in EELV resulting in increase in end-tidal tracer gas concentration. Flow is highly erratic with or without forced breathing or hyperventilation with CO2 outside 4-6% range. No evidence of leak. End of test criteria met (three tidal breaths under the target concentration).

Supplemental Figure 4 (continued): Examples of characteristics of usable and not acceptable or usable MBW tests on the % Nitrogen, Flow (L/s), and Volume (L) versus Time (s) traces. (continued on next page).
Supplemental Figure 4 (continued): Examples of characteristics of a not acceptable or usable MBW test on the % Nitrogen and Flow (L/s) versus Time (s) traces.

Not acceptable or usable due to leak, start of test criteria not met, or end of test criteria not met: Inadequate time between trials for gas concentrations to re-equilibrate. Evidence of leak during washout before end of test criteria. Leaks are visible as large or small spikes in end-tidal tracer gas, non-continuous decline in end-tidal tracer gas, or no change in end-tidal tracer gas over multiple breaths. End of test criteria not met: trial does not have three tidal breaths under the target tracer gas concentration. If a trial has any of the three conditions above, the test will be deemed not acceptable, irrespective of breathing pattern.
**Supplemental Figure 5:** Display of volume–time spirograms applicable to multiple breath washout and helium dilution, showing examples when the patient is not switched into the circuit at FRC. 

a) The patient was turned into the circuit near the end of tidal inspiration, at a lung volume higher than the functional residual capacity (FRC), and the volume difference ($\Delta V$) would be subtracted.

b) The patient is turned into the circuit at a lung volume below FRC, and the $\Delta V$ would be added.

c) The patient was turned into the circuit above the true FRC, and the $\Delta V$ would be subtracted.
Comprehensive technical standards across all age ranges for measurement of airway resistance by body plethysmography do not exist for equipment (e.g., volume drift, electronic compensation during tidal breathing), software (e.g., how the slope is calculated), technical acceptability and patient performance (e.g., breathing rate, flow rate, body position, characteristics of acceptable flow vs pressure loops), or quality control (e.g., use of known resistors for calibration). This supplemental section is not intended as a technical standard. Rather, best practices based on the experience of task force members and a non-systematic review of the English-language literature is provided, with emphasis on the need to separate measurement of airway resistance from lung volumes, the methods that lack standardisation, and a call for development of an evidence base to inform a future standard. A consistent approach should be used to compare values within and between patients. We provide published details on reference equations from English-language publications because the task force recommends that when applying reference equations, the methods used for their derivation should match those used to make the measurements as closely as possible.

**Background**

The body plethysmograph (body box) is also used to measure airway resistance (Raw) during breathing and/or its reciprocal airway conductance (Gaw = 1/Raw), as this is a simple addition to the lung volume assessment. Raw may be sensitive to small and rapid changes and thus can play a part in recognition of response to a bronchodilator as well as contribute to the diagnosis and differentiation of obstructive airways diseases. The principle for measuring Raw is the same as for the measurement of lung volumes: the change in air pressure in the cabin of the plethysmograph correlates with the change in alveolar pressure. The actual parameter being measured during open shutter panting is specific Raw (sRaw). sRaw (kPa.s) is the ratio of alveolar pressure change assessed via change in lung volume (or equivalently, change in cabin pressure) to change in flow rate. Graphically, mouth flow as recorded from the flow measuring device (e.g. from a pneumotach) is on the y-axis versus box pressure (produced by thoracic compression and decompression) on the x-axis. Individuals with airflow obstruction often have open loops during expiration. Raw (kPa.L⁻¹.s) is the ratio of sRaw to TGV.

Raw and its associated TGV must be measured independently of the lung volumes. TGV manoeuvre to ensure accuracy of lung volumes and airway resistance because the optimal panting frequencies are different and increased time on the mouthpiece increases opportunity for leak which can compromise accurate measurement of lung volumes. In addition, some patients may not tolerate the extended time on the mouthpiece and with the door closed when measurement of lung volumes and Raw are combined.

**Measurement technique**

Airway resistance is measured at FRC, the normal lung volume at which the subject breathes. In 1956, Dubois et al. described the technique of rapid shallow breathing (i.e. panting) in adults to minimise the temperature, saturation and respiratory quotient effects of tidal breathing, and to improve the signal to drift ratio given the shorter breathing cycles [31]. We suggest a pant rate between 1.5-2 per second with a Vt of 50 to 150 mL. Rapid panting ensures full opening of the vocal cords but increases turbulent flow [32]. Airway resistance increases exponentially when flow is turbulent [33]. Varying breathing rates may also change airway
resistance in the setting of unequal time constants. The combined technical and physiological effects have been observed to lead to airway resistance measurements that are about 10% lower with panting compared to tidal breathing [34], higher [35], or the same [36]. The rapid panting technique has a tighter CV and less variability of Raw and SGaw than the slow (0.5-1.0 per second) and gentle tidal breathing method (0-0.5 per second) in healthy persons [37]. The difference in results between tidal breathing with or without a rebreathing bag in the absence of compensation was quantified in one study [38]. Current hardware and software reportedly have improved integrated algorithms to compensate for thermal and humidification effects so that sRaw can be measured during slightly enhanced tidal breathing at normal resting FRC without a rebreathing bag and without the need for rapid panting as originally described by Dubois et al [39]. However, these algorithms lack published validation in adults, with at least one study finding a significant bias albeit with older equipment [40].

1) Establish a stable FRC. Stable FRC is defined as having at least three tidal breaths with max-min end tidal volume within 15% of the tidal volume.

2) Instruct the patient to pant at a rate of 1.5-2 per second with the shutter open.

3) To measure the lung volume associated with the airway resistance measurement, the shutter should be closed within a short time after having obtained acceptable open-shutter loops to ensure the proper association between loops and TGV. The closed shutter manoeuvre must follow rather than precede open shutter panting because lung volume can drift and the best airway resistance loops are typically obtained towards the end of open shutter panting. As noted in the main text, the pant frequency during measurement of TGV is slower, at 0.5-1 per second.

4) The median value of up to five technically acceptable loops should be taken. The aim should be to report the mean of the results from at least three acceptable manoeuvres.

Special considerations in children
In young children (from about 2 years of age) who would not be able to perform reliable spirometry, measurement of airway resistance is useful for discriminating lung disease. A mouthpiece and nose clip can be used, but also the use of a modified facemask is possible. Standards specific to plethysmographic measurement of airway resistance in infants during tidal breathing have been published [41]. Standards for children age 3-10 year also recommend tidal breathing [42]. Both of these standards recommend the use of effective specific airway resistance (sRaweff) as it integrates data throughout the breathing cycle. Despite electronic compensation of alterations in temperature and humidity during tidal breathing without use of a rebreathing bag, compensation is not complete and children are still encouraged to breathe more rapidly than normal (e.g. ≥ 30 breaths per minute) to minimise the effects [42, 43]. In a 2005 study in infants, electronic compensation was found to be even less adequate than in older children, with a smaller equipment dead space postulated as one reason [44]. Studies in children note that there is inter-centre variability in airway resistance (and other plethysmographic measures) despite extensive standardisation procedures [45], which is likely worsened by lack of standardisation between centers in clinical practice [46].

Table 6: Further recommendations for sRaw measurements
Equipment:
- Use an appropriately sized mouthpiece and noseclip
- Always use a bacterial filter
  - Ensure calibrations are performed with filter *in situ*, and internal settings have accounted for the filter.

Measurement
- Ensure sitting upright, with no leak between the lips and mouthpiece
- Prior to commencing test, sufficient time is allowed for thermal stabilisation with the subject sitting in the plethysmograph.
- Cheek supported with hands.
  - While not strictly necessary if no occlusion manoeuvres are performed, this is good practice for when plethysmographic assessments that include measures of FRC.
- Perform Raw manoeuvre with TGV to calculate $s_{Raw}$ and $s_{Gaw}$
  - Quiet stable breathing followed by shallow panting (1.5 - 2.0 per second) or tidal breathing, followed by shutter closure
- Perform at least 3 manoeuvres yielding at least 5 panting loops each.

Quality Control:
- Use the automatic computer selected tangent
- Examples of normal and abnormal open shutter tracings are available in [47]

$s_{Raw}$ Outcomes:
- Report $s_{Raw\text{eff}}$ as the main outcome measure
  - $s_{Raw\text{tot}}$ should be recorded where available
  - Breathing frequency, peak expiratory and inspiratory flow (PEF and PIF respectively) should be recorded as QC outcomes
- FRC and VT should be reported as some methods compute Raw from FRC+VT/2
- Report the Median of the median: Select the median (middle) breath from the median trial of 3 technically acceptable sets of 5-10 breaths
- Analysis of the form of breathing loops can provide relevant pathophysiological information but techniques for characterization are not standardised.
Methods to determine the slope of the flow vs box volume (equivalently flow vs box pressure) loop

The method used for determination of $s_{Raw}$ (inverse of the slope of the flow vs pressure loop) should be stated and match what was used in the derivation of the reference equations applied. A summary of methods follows and some examples are given in Supplemental Figure 6.

$s_{Raw_{eff}}$ and $s_{Raw_{tot}}$:

- A review by Criee et al. notes that total (apparent) airway resistance ($Raw_{tot}$) and effective that $Raw_{tot}$ may represent more peripheral obstruction and may be more sensitive to changes in the airways because it is based on just two points of extreme of the flow vs box volume loops. However, they recommend $Raw_{eff}$ because it is expected to be less variable, as it is based on integrating data across the breathing cycle, a view supported by data presented in a study by Matthys and Orth [48].
- Matthys and Orth 1975 [48] introduced a power-based method yielding what they called effective airway resistance ($Raw_{eff}$). $Raw_{eff}$ was defined using an electrical circuit analogy: 1) power for current flow through a resistor is $R*I^2$. 2) They defined an effective flow (current) by analyzing flow-volume curves. 3) They defined the power to overcome airway resistance through pressure and volume measurements from the box and spirometer, as well as ventilated lung volume as $FRCH_{He}+VT/2$. 4) From these the effective flow and power, they calculated an effective airway resistance from the equation $R=Power/(flow^2)$. One can then use lung volume to calculate specific effective airway resistance ($s_{Raw_{eff}}$) and display an equivalent slope on the traditional flow vs box volume loop. Alternatively, as proposed later by others, specific effective airway resistance can be computed first by taking the area of the tidal volume vs box volume curve and dividing by the area of the tidal flow vs volume curve. Their study obtained data during tidal breathing through a rebreathing bag at ~22 breaths per minute.
- Total apparent airway resistance (apparent airway resistance), or $s_{Raw_{tot}}$, is calculated by connecting the points of peak inspiratory and expiratory body box volume change [48, 49].
- Matthys and Orth found that $Raw_{tot}$ agrees very well with effective airway resistance, whereas the method of Jaeger and Otis 1964 below agrees less well.
- Stocks et al. 2001 [41] suggest that $s_{Raw_{eff}}$ is equivalent to regressing through all the data points of the flow vs pressure loop if the sampled data points are equidistant. Unequal distribution of sampled points such as with rapid flow and minimal volume change at the beginning of inspiration are expected to result in small differences between $s_{Raw_{eff}}$ and regression of the loop.

Methods of slope determination less commonly seen in recent literature:

- In Dubois’ historic advance in JCI 1956 [39], the slope was determined from the line connecting 1 L/s of inspiratory flow to 1 L/s of expiratory flow. Criticisms of this approach are that generation of ≥ 1 L/s flow is not guaranteed to always occur, and that using only two data points introduces a source of variability.
- Described in Bisgaard [49]:
  - $s_{Raw_{0.5}}$ or 0.2: line connecting the points where flow reaches a fixed flow (L/s) (similar to Dubois et al. above)
Jaeger and Otis in 1964 [35] state their goal was to develop a method for measuring airway resistance during tidal breathing. They present an equation relating the area of the spirometer volume change vs box volume change to coefficients of laminar and turbulent flow with a theoretical sinusoidal input. Assuming the turbulent resistance is small enough to be ignored compared to the laminar resistance, an equation is given for airway resistance as a function of the area of this volume vs volume loop and the mean lung volume (FRC+VT/2). From this, a slope can be back-calculated.

Supplemental Figure 5: Examples of different methods for determining the slope of the flow vs box volume loop for determination of airway resistance. $s_{Raw_{tot}}$ (green) is obtained from the line connecting the flow points at maximum change in plethysmographic volume (pressure). If there is more than one maximum, the point associated with the greatest airflow is used. $s_{Raw_{0.5}}$ (black) is obtained from the line connecting the points where the flow reaches 0.5 L/s. $s_{Raw_{Vmax}}$ (blue) is obtained from the parameter line connecting the maximum flow points. $s_{Raw_{mid}}$ is obtained from the line connecting the midpoints of the lines formed by the intersections of the loop at the flows of 0.5 L/s. Adapted from figures and descriptions in [49, 50].
Reference values for airway resistance from body plethysmography
The availability of reference values for airway resistance parameters was limited to relatively small sample sizes (Table 7) until recently and the normal range is much larger than it is for spirometric measures. A set of reference equations for adults with a reasonable sample size is available [51]. For children, reference equations for specific airway resistance from a large sample size have been developed by J. Kirkby et al. [52]. This group noticed significant methodological differences between centres that perform sRaw measurements [46]. Therefore, they made an important call for the use of standardised methodology together with standardisation of internal settings in the equipment. Another study found that significant inter-centre variability remains despite extensive standardisation, some of which was related to factory settings inaccessible to the user, suggesting that local biological controls are essential [45].

Table 7: Characteristics reported in selected English-language healthy reference value publications for airway resistance from body plethysmography:

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Population</th>
<th>Equipment</th>
<th>Breathing pattern</th>
<th>Slope method</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briscoe and Dubois 1958 [31]</td>
<td>8 children age 4-13 yr, 7 adult females, 11 adult males</td>
<td>Panting</td>
<td>Line connecting 1 L/s of inspiratory flow to 1 L/s of expiratory flow</td>
<td></td>
<td>Method of Dubois et al. 1956. Apparatus dead space and half the volume of the tracheobronchial tree subtracted from FRC. Reported fixed sGaw range across all subjects</td>
</tr>
<tr>
<td>Brunes and Holgrem 1965 [53]</td>
<td>60 adult females</td>
<td>2 breaths per second</td>
<td>sRaw0.5</td>
<td>Method of Dubois et al. 1956. Head erect Equipment dead space subtracted</td>
<td></td>
</tr>
<tr>
<td>Von der Hardt et al. 1976 [54]</td>
<td>82 children</td>
<td></td>
<td>Slope of the total loop</td>
<td>Apparatus dead space subtracted</td>
<td></td>
</tr>
<tr>
<td>Springer et al. 1993 [55]</td>
<td>15 infants</td>
<td>Rebreathing bag</td>
<td>Tidal breathing</td>
<td>sRaw calculated at multiple points on the loop</td>
<td></td>
</tr>
<tr>
<td>Klug and Bisgaard 1998 [43]</td>
<td>121 2-7 yr White children (61 males, 60 females)</td>
<td>facemask with mouth opener</td>
<td>Tidal breathing 30-45 breaths per minute</td>
<td>sRawtot, sRaw0.5, sRaw0.5 Median of 5 loops</td>
<td>Reference values independent of age, sex or height. Accompanied by an adult who performed a slow expiratory manoeuvre. Later pooled with data from 105 additional children in 2009 [56].</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Equipment/Protocol</td>
<td>Output Measures</td>
<td>Notes</td>
<td></td>
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</tr>
<tr>
<td>Manzke et al. 2001 [57]</td>
<td>211 male and 186 female children 6-16 yr</td>
<td>Jaeger MasterLab</td>
<td>sRaw$<em>{eff}$ and sRaw$</em>{tot}$ Best of 3-5 measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia-Rio et al. 2009 [58]</td>
<td>189 adult females, 132 adult males</td>
<td>Rebreathing bag</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirkby et al. 2010 [42]</td>
<td>1,908 children 3-10 yr of European descent</td>
<td>Jaeger plethysmograph (≤ version 4.01), specialised mouthpiece and noseclip</td>
<td>Tidal breathing 40-45 breaths per minute</td>
<td>sRaw$<em>{tot}$ and sRaw$</em>{eff}$ Mean of at least 5 results, Apparatus dead space subtracted</td>
<td></td>
</tr>
<tr>
<td>Koch et al. 2012 [51]</td>
<td>275 adult males, 411 adult females</td>
<td></td>
<td>sRaw$_{tot}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piatti et al. 2012 [59]</td>
<td>249 adult females, 268 adult males</td>
<td>Werner Gut</td>
<td>sRaw0.5</td>
<td></td>
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<tr>
<td>Verbanck et al. 2016 [60]</td>
<td>124 adult females, 128 adult males</td>
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<tr>
<td>Kraemer et al. 2021 [61]</td>
<td>270 adults (72 males, 198 females), 38 infants (24 males, 14 females), 44 children (23 males, 21 females)</td>
<td>Master Screen Body, Jaeger Tidal breathing</td>
<td>sRaw$_{eff}$ Median of 5 results</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References


