

**ERS/ATS WORKSHOP REPORT SERIES**

# Multiple-breath nitrogen washout techniques: including measurements with patients on ventilators

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The determination of lung volumes is an important part of the respiratory management of infants, children and adults. In all age groups, lung volume measurements can help in diagnosing respiratory disorders, in evaluating response to therapy, and in finding suitable ventilator settings with respect to rate and ventilatory pressures [1–4]. Lung volume is also an important variable when lung mechanics are measured [5] because specific compliance and specific resistance are normalized by lung volume, *i.e.* the functional residual capacity (FRC). In addition, the most fundamental interest in lung volume measurements in infancy and childhood relates to the assessment of normal and abnormal lung growth [6]. Similarly, maximal expiratory flows in partial flow-volume loop manoeuvres performed using the rapid thoracoabdominal compression technique require information about the lung volume. The lack of co-operation and the size of the subjects to be studied in this age group (and hence of the lung volumes to be measured) require miniaturization and special adjustments of the methods and apparatus.

Currently, the FRC (end-expiratory volume) is the only lung volume that can be accurately, repeatedly and reliably measured in infants and small children, and also in adults unable to co-operate. Hence, it is the only lung

volume that can be routinely determined for clinical reasons either in ventilated patients of all ages or in paediatric out-patient clinics. Other lung volumes, such as total lung capacity (TLC) and residual volume (RV), can also be measured in such cases, but the techniques are employed mainly for research, and sometimes require an endotracheal tube (ETT). Consequently, techniques for determination of these volumes have not yet become bedside procedures.

## Definition

The volume of air contained in the lung at end-tidal expiration is defined as functional residual capacity and, in healthy adults, this volume is usually determined by the passive balance between the elastic forces of the lung and chest wall. In newborns, infants, and some adults with lung disease, however, factors such as laryngeal braking, postinspiratory muscle activity during expiration [7, 8], and a relatively rapid respiratory rate [9] may result in the end-expiratory lung volume being actively elevated above the elastic equilibrium volume. In patients with obstructive lung disease, FRC may be elevated by the presence of trapped gas.

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### Methods for determining FRC

Lung volumes were first measured using a hydrogen gas dilution technique about 200 yrs ago. Helium replaced hydrogen for safety reasons, when clinicians started to use the test [10]. Currently, FRC can be measured by two major techniques: plethysmography (utilizing adult and infant body-boxes), and gas dilution or wash-out techniques. The most commonly used are helium (He) dilution (a closed-circuit method), and nitrogen (N<sub>2</sub>) washout (in its modern form, an open-circuit method). Other gases can be employed, and, over the past decade, a new method has been developed using sulphur hexafluoride [11–14].

### Choice of method

Body plethysmography measures the total gas in the thoracic cage (and the small amount in the abdominal and oral cavities), irrespective of whether the gas is freely communicating or trapped behind obstructed airways. The gas dilution techniques can measure only that gas which is freely communicating.

The choice of technique has traditionally been determined by the specific reasons underlying the need for lung volume measurements, and tempered by financial constraints and availability of local expertise and equipment. If the primary interest is alveolar growth and development, or the assessment of total gas volume in a child with airway disease, then plethysmography may be the most relevant technique. By contrast, if one is interested in the accessible, rather than compressible lung volume, *i.e.* the functional lung volume available for gas exchange, then one of the gas dilution techniques may be more appropriate.

Under certain circumstances, it may also be rational to use both techniques, depending on the clinical entity that is to be measured. For example, in lung cysts and lobar emphysema, use of both FRC measured in an infant plethysmograph (FRC<sub>pleth</sub>) and a gas dilution technique will allow quantification of the amount of gas trapped. Except in the smallest of infants, sedation is required for each technique up to the age of 4–6 yrs.

While detailed reviews of the various lung volume measurement techniques are provided elsewhere in this series, a few points concerning each method are relevant here.

#### *FRC measured by plethysmography (FRC<sub>pleth</sub>)*

While often viewed as the "gold standard", the expense and complexity of plethysmography, together with the relative dearth of systems with computer driven calibration and operating packages (which make it very labour-intensive) and the fact that it is not usually suitable for use in very sick patients or on the intensive care unit (ICU), has limited its widespread application. EDBERG *et al.* [15] have reported its safe use in the neonatal ICU, but the actual determination of lung volume was performed by a nitrogen washout technique.

#### *FRC measured by helium dilution (FRC<sub>He</sub>)*

This technique [16–20] is the most widely used method for determining resting lung volume in spontaneously

breathing infants, children and adults. The method is based on the principle of gas equilibration. Gas containing a known concentration of He, as an indicator, is equilibrated between an unknown lung volume and a closed system, which has an in-line reservoir of known volume, by rebreathing. When equilibration has been achieved, the He concentration is the same in all parts of the system, and the final concentration of He in the reservoir can be determined. Assuming mass balance, the total volume of its distribution can, thus, be calculated from the initial concentration and volume of distribution of the He, and its final concentration. Subtracting apparatus volume from total volume gives lung volume. The equipment needed to perform the test is simple, reliable, relatively cheap (compared with plethysmography), and suitable for bedside measurements, but still requires considerable operator training and precision with O<sub>2</sub> addition and CO<sub>2</sub> removal, if reliable results are to be routinely obtained [21, 22] and serious errors in calculated FRC avoided.

Measurements of FRC by He dilution are highly reproducible, with a coefficient of variation (COV) of 4%, although there appears to be greater variability under the age of 1 month [19].

#### *FRC measured by nitrogen washout (FRC<sub>N<sub>2</sub></sub>)*

The N<sub>2</sub> washout method for measuring lung volumes was developed into a clinical technique by DARLING and co-workers [23–25] in a series of papers published in 1940. The principle of the technique is that N<sub>2</sub> is washed out of the body by having the subject breathe 100% oxygen, starting the first inspiration of O<sub>2</sub> from FRC. Expired volume is collected over 7 min and initial and final alveolar N<sub>2</sub> fractional concentrations and N<sub>2</sub> concentration in the collected expirate are measured. FRC is calculated as follows:

$$\text{FRC} = \frac{(\text{volume N}_2 \text{ washed out}) - (\text{N}_2 \text{ tissue excretion})}{\text{initial} - \text{final lung N}_2 \text{ concentration}} \quad (1)$$

Nitrogen excreted from the tissues is estimated from standard tables of tissue N<sub>2</sub> elimination adjusted for body weight. This is not negligible. In a 70 kg man with 20% body fat, tissue N<sub>2</sub> stores may amount to 1.3 L [26]. However, the excretion rate is slow since about 70% of the tissue stores receive only 10% of the blood flow. Tissue excretion rates of N<sub>2</sub> were measured in normal individuals, who had first hyperventilated to remove alveolar nitrogen stores [24], and were then applied in the above equation. DARLING and co-workers [24, 25] assumed from their normal subjects that the total N<sub>2</sub> eliminated from the tissue stores during 7 min of O<sub>2</sub> breathing was approximately 220 mL, and made no adjustments for body weight in their subsequent patients. Estimated alveolar N<sub>2</sub> concentrations were measured at the beginning and end of expired gas collection during a forced exhalation. The N<sub>2</sub> concentration at the end of the O<sub>2</sub> breathing was used as an estimate of mixing efficiency in the lung: the higher the fractional N<sub>2</sub>, the lower the mixing efficiency. A Van Slyke apparatus was used for measuring N<sub>2</sub> concentrations: hence, only a limited number of measurements were possible. In modern

terms, this technique suffers from technical difficulties that make it impractical. Any inaccuracy in the measurement of the bag volume and the final N<sub>2</sub> concentration will cause a significant bias. It is apparent that the final N<sub>2</sub> concentration may be very low because of dilution of the gas with a large amount of O<sub>2</sub>, so that even an error of less than 1% in determination of N<sub>2</sub> concentration will be very significant.

Because of the limitations of the gas collection method, efforts have been directed to develop automated techniques, which will allow immediate results without the need to collect gas for future analysis of volume and N<sub>2</sub> concentration. The major breakthrough towards accomplishing this goal came with the introduction of the microprocessor-based personal computer (PC) and rapidly responding gas analysers (including respiratory mass spectrometers) [4, 27, 28], which enabled very frequent gas and flow sampling (up to several 100 samples·s<sup>-1</sup>), and real-time data processing and integration of these variables. This gave a major stimulus towards the development of true open-circuit techniques.

In the open-circuit methods, the patient is switched to breathing 100% O<sub>2</sub>, and from this point the volume of N<sub>2</sub> exhaled is determined by integration with respect to time of the instantaneous N<sub>2</sub> concentration flowing in the exhalation circuit multiplied by the instantaneous flow. The latter obviously changes continuously during washout as the patient breathes:

$$VN_2 = \int V'N_2(t) \cdot dt \quad (2)$$

where:  $V$  = volume;  $N_2$  = mean nitrogen concentration in the volume;  $V'$  = flow and  $N_2(t)$  = instantaneous concentration of nitrogen.

In order to measure gas flows, pneumotachographs may be incorporated into the breathing circuits. However, variations in temperature and viscosity during gas flow through the pneumotachograph may influence gas flow measurements by as much as 10–15%.

Whilst DuBois *et al.* [29] were able to show close agreement between FRC measured by the plethysmographic technique and the 7 min N<sub>2</sub> washout in normal adult subjects, in patients with severe emphysema, the plethysmographic method yielded an FRC which ranged up to 3.6 L more than that estimated from the 7 min N<sub>2</sub> washout. The difference was referred to as trapped gas, the name suggesting an alveolar compartment in the lungs that is not ventilated. EMMANUEL *et al.* [30] subsequently pointed out that the primary cause of this underestimation of FRC was not from actual gas-trapping but resulted from the inability to measure mean alveolar N<sub>2</sub> concentration accurately in patients with emphysema after only 7 min of O<sub>2</sub> breathing. Measurements of alveolar N<sub>2</sub> concentration during a forced exhalation were highly weighted in favour of the more normally ventilated regions of the lung, thereby giving an estimated final N<sub>2</sub> concentration which was low with respect to the true mean. This leads to an overestimation of the change in alveolar N<sub>2</sub> concentration in the FRC equation, and thereby causes an underestimation of the lung volume.

EMMANUEL *et al.* [30] modified the method to a 15 min washout with oxygen with appropriate corrections for additional tissue N<sub>2</sub> washout. This gave significantly

higher estimates of FRC in patients with severe emphysema, and the difference between the 7 and 15 min N<sub>2</sub> washouts gave estimates of trapped gas similar to that measured by comparing the 7 min washout with the plethysmographic method. The method has now been further refined with on-line continuous integration of the product of the expired nitrogen fraction ( $FE_{N_2}$ ), obtained from a respiratory mass spectrometer or nitrogen meter, and flow ( $V'$ ), provided by a pneumotachograph, as mathematically described in Equation 2.

Under this special circumstance of prolonged O<sub>2</sub> breathing at between 5 and 15 min of O<sub>2</sub> breathing, the excretion rate of N<sub>2</sub> corrected for body tissue elimination approaches a monoexponential decay with time, which can be expressed as:

$$(V'N_2)_{t2} = (V'N_2)_{t1} \cdot e^{-k\Delta t} \quad (3)$$

where:  $k$  = exponential time constant, *i.e.* ventilation per unit volume of the slowly ventilated space;  $\Delta t$  = time interval ( $t2 - t1$ ) between  $(V'N_2)_{t2}$  and  $(V'N_2)_{t1}$ ; and  $e$  = base of the natural logarithm. Taking the natural log of both sides and solving for  $k$  gives:

$$k = \frac{\Delta \ln(V'N_2)}{\Delta t} \quad (4)$$

which is the ratio of alveolar ventilation per alveolar volume of the slow compartment. The volume of N<sub>2</sub> at the end of 15 min oxygen breathing can be estimated by extrapolation of the late monoexponential N<sub>2</sub> elimination curve to infinity as follows:

$$N_2 \text{ (remaining)} = (V'N_2)_{t=15} \cdot \int_0^\infty e^{-kt} = \frac{(V'N_2)_{t=15} \cdot e^{-15k}}{k}$$

Therefore:

$$FRC_{BTPS} = \frac{\int V'N_2 \cdot dt + [(V'N_2)_{t=15} \cdot e^{-15k}] \cdot k^{-1}}{0.79} \cdot 1.21 - DS_{BTPS} \quad (5)$$

where:  $DS$  = apparatus dead space, containing room air at the start of the procedure; and 1.21 = conversion factor from volume in standard temperature and pressure, dry (STPD) to body temperature, pressure and saturation (BTPS).

The volume of the slowly ventilated compartment at the start of O<sub>2</sub> breathing can be estimated by extrapolation of the late linear relationship of  $\ln(V'N_2)$  with respect to time back to its y-intercept at zero time, to yield  $\ln(V'N_2)_0$ . Then, integrating the exponential decay of  $\ln(V'N_2)$  from zero time to infinity and dividing alveolar N<sub>2</sub> concentration yields:

$$\text{Volume of slow space}_{(BTPS)} = \frac{(V'N_2)_0}{0.79 k} \times 1.21 \quad (6)$$

and

$$\text{Ventilation of slow space}_{(BTPS)} = \frac{(V'N_2)_t}{0.79 k} \times 1.21 \quad (7)$$

### Standards for lung volume measurement by gas dilution/washout techniques

The American Thoracic Society (ATS) has not previously recommended standards for the measurement of lung volumes, but the European Coal and Steel Community (ECSC) did so for the helium dilution method in 1983 [31], and the European Respiratory Society (ERS) endorsed the 1993 update of these European standards [32]. At this point, formation of new standards requires a balance between: 1) accommodating an established base of older instruments, using traditional manual techniques; and 2) requiring the development and purchase of expensive new instruments, fully automated by PCs with extensive new quality assurance programmes.

A few commercially available systems use innovative or alternative techniques, which have potential advantages over the standard techniques given in this document. Such innovation should be encouraged: however, it is the responsibility of manufacturers to demonstrate that the lung volumes reported by such new instruments do not vary substantially from those obtained by investigators who developed reference equations. The methods in this document outline standards against which comparability of new systems may be demonstrated.

### Nitrogen washout test for adults and older, co-operative children

The open circuit, multiple-breath nitrogen washout test used to measure lung volumes should not be confused with the single-breath nitrogen test, also known as the "closing volume" test. Both tests use similar instrumentation, both can give measurements of FRC and the degree of nonuniformity of gas distribution in the lungs, but the multiple-breath test more accurately measures absolute lung volumes.

### Equipment

The multiple-breath nitrogen washout test was originally developed using a very large (120 L) manually operated Tissot spirometer. However, most pulmonary function laboratories now use commercially available systems, all of which use a small pneumotachograph, and an integrator connected together with the N<sub>2</sub> analyser to a PC [33].

1. A breathing valve controls whether the patient breathes room air or inhales 100% oxygen. Valve dead space should be less than 100 mL.
2. The oxygen source is either a compressed O<sub>2</sub> tank connected to a demand valve, or a large, gas-impermeable bag filled with dry 100% oxygen. One-way valves in the circuit minimize rebreathing. The demand valve should not require more than 0.2 kPa (2 cmH<sub>2</sub>O) pressure to start the flow. It should be able to deliver up to 6 L·s<sup>-1</sup> of flow, and its resistance should not exceed 1.5 cmH<sub>2</sub>O·L<sup>-1</sup>·s<sup>-1</sup> of flow.
3. A fast-responding nitrogen analyser measures N<sub>2</sub> concentration continuously at the mouthpiece. An ionizing chamber type of N<sub>2</sub> analyser requiring a vacuum pump is commonly used, but a respiratory mass spectrometer may also be utilized (see below). The linearity

of the analyser should be accurate to within 0.2% over the entire range of 1–80% N<sub>2</sub>. The 95% response time should be less than 25 ms (after phase lag correction) to a 10% step change in N<sub>2</sub> concentration. Adequacy of the vacuum should be monitored with a gauge or limit switch.

4. A pneumotachograph should be used to measure air-flow at the mouth. The pneumotachograph is connected to a differential pressure transducer by a short length of tubing to optimize frequency response, and then to an analogue-to-digital (A-D) converter and microprocessor. The signal is then digitally integrated to obtain exhaled volume. The pneumotachograph should be accurate to within 3% of reading at static flows ranging 0–6 L·s<sup>-1</sup>, and should not allow condensation of moisture from exhaled air to reduce accuracy. Flow accuracy should be maintained over the range of oxygen/nitrogen concentrations found during testing.

5. The temperature both of the pneumotachograph and the ambient air should be measured automatically every 10 s with 0.5°C accuracy, in order to provide an accurate BTPS correction both for exhaled and inhaled air.

6. An A-D converter with a sampling rate of at least 40 samples·s<sup>-1</sup> (every 25 ms) per channel should be used to digitize the flow and N<sub>2</sub> signals, with a resolution of at least 1:1,024. The microprocessor must adjust for the lag time difference between the flow and N<sub>2</sub> concentration signals, before multiplying them together to obtain the amount of N<sub>2</sub> exhaled every 25 ms. Accurate phase lag adjustment may require sampling at rates which exceed the minimum value given previously [34]. When a Fleisch-type pneumotachograph is used, the microprocessor must also correct the measured flow for the changing viscosity of the exhaled gas mixture. Some systems use a rebreathing bag in place of a pneumotachograph or spirometer [35], but these have not been validated by comparisons with standard techniques.

### Quality control

1. Before each patient is tested, the N<sub>2</sub> should be zeroed and a three-point calibration checked using: 100% O<sub>2</sub> (zero nitrogen); a calibration gas of 40% N<sub>2</sub>; and room air. The three values measured should be accurate to within 0.5% before proceeding.
2. Before each patient is tested, computerized systems should automatically check: vacuum level; pneumotachograph temperature (38–40°C); flow (zero); and N<sub>2</sub> (79–81%) signal levels. The system should warn the technician and prevent patient testing if these are out of range.
3. The computer must enable a volume calibration check of the pneumotachograph and digital integrator (with the heater off). This should be verified during the 24 h prior to testing a patient, or after cleaning the pneumotachograph. The exhalation volumes should be measured by injecting 3.0 L of room air both slowly (~3 s) and quickly (<1s). The resulting lung volumes should both be within 3% of 3.0 L ambient temperature and pressure, saturated (ATPS) (no BTPS correction is necessary). The inhalation volumes should then be similarly verified using 100% O<sub>2</sub> sucked from the demand valve or oxygen bag into the calibration syringe.

4. A technician who has normal lung function should be tested at least once per week [36]. The results and percentage error should be calculated, graphed and reported. If the error is more than 5% (or greater than  $\pm 3$  standard deviations of the mean of the 10 previous measurements) [37, 38] then the problems should be diagnosed, repaired, documented, and the technician successfully tested again before testing any patients.
5. The  $N_2$ /time and volume/time tracings from patient tests should be examined (ideally automatically) for sudden or slow inward or outward leaks, and reproducibility of the end-tidal volumes, inspiratory capacities and slow vital capacities.
6. The stability of the nitrogen and flow signals (when no change is expected) should be examined for excessive noise and drift. The inspired  $N_2$  concentration should remain near zero. Ideally, the shape of the end-expiratory  $N_2$  signal should be examined for a smooth decline and plateau during the test, bearing in mind that the plateau, typically, does not occur in patients with severe airways obstruction. Sudden decreases in  $N_2$  concentration indicate inward leaks (usually around the mouth-piece), and the test must then be repeated.
7. If the final  $N_2$  concentration is more than 1.5% at the end of the test, the value should be given in the final report, together with the warning that the absolute lung volumes (FRC and TLC) may be inaccurate. The results should not be reported if a leak was noted or if the results are not physiological (<30% or >200% of the predicted TLC).
8. For each patient, the technician should document the following: eardrum perforation; problems with leaks around the mouthpiece; apparent degree of effort during the slow vital capacity manoeuvres.

### Nitrogen washout test for infants and young children

#### FRC measurement during spontaneous ventilation

As noted previously, pneumotachographs can be incorporated into the breathing circuits, but variations in gas temperature and viscosity during flow measurements may create an error of 10–15%. In paediatric practice, this creates an error of unacceptable magnitude. In 1984, SJÖQVIST *et al.* [39] overcame this difficulty by placing the infant in a face-out body-box. The  $N_2$  concentration in exhaled gas was analysed by a  $N_2$  analyser incorporated into the exhalation circuit, and the flow was derived from a pneumotachograph incorporated into the wall of the body plethysmograph. The flow through the pneumotachograph resulted from the patient's breathing and volume changes inside the box, the only outlet from which was the pneumotachograph. Therefore, the flow was not influenced by changes of temperature, humidity and viscosity, and the lung volume was given in BTPS. Breath-by-breath integrations of flow and  $N_2$  concentrations were used to calculate the amount of  $N_2$  washed out. One problem with this system is that any difference in the response times between the  $N_2$  signal and the flow signal resulting from differences in time constants of the apparatus will affect the results. The

main disadvantages are that the system is cumbersome and has not been automated commercially. It is, therefore, difficult to use outside laboratory conditions and, consequently, the method has never been widely accepted.

In 1985, GERHARDT *et al.* [40] provided a method to overcome the change in gas flow in nonventilated infants and children. They used an open washout system, to which a constant background  $O_2$  flow was delivered. The patient inhaled from and exhaled to that circuit with background flow. Although the instantaneous flows of the washout circuit change continuously as the subject breathes, the average flow leaving the system over time remains unchanged, because the volume of gas subtracted during inspiration is added back to the system during exhalation (this is true as long as the temperature and humidity of the inhaled and exhaled gas are equal, a condition which is easy to meet by using a humidifier). Because the method ignored the instantaneous change in flow and used only the average constant flow for calculation, it was essential that sampling of  $N_2$  for concentration measurements would "see" a continuous decrease of  $N_2$  concentration as the washout proceeded, without the effect of the respiratory phase. This was achieved by incorporating a mixing chamber in the exhalation circuit, before the sampling port from which mixed expired gas was sampled for  $N_2$  analysis. Under these conditions, if flow is constant, then the volume of  $N_2$  washed out is obtained from Equation 2:

$$VN_2 = V' \int N_2 dt \quad (8)$$

The technique was made more reproducible and accurate by the development of a two-point calibration system by SIVAN and co-workers [4, 41].

#### Assumptions and limitations of the method

1. The background flow should be higher than the peak inspiratory flow of the subject, so that no gas is rebreathed into the mixing chamber/sampling port area. Adjusting the background flow to just slightly higher than peak inspiratory flow allows flow to be lower in smaller infants and, thus, makes the system more sensitive to the smaller amounts of  $N_2$  exhaled. Hence, the size of the patient is not a limiting factor in the accurate measurement of FRC with this technique.
2. The time required for washout of the  $N_2$  from normal lungs breathing room air (fraction of inspired nitrogen ( $F_{I,N_2}$ )=0.79 approximately) is about 60 s. Patients, especially infants and small children, with restrictive lung disease and those breathing elevated inspired oxygen concentrations may wash out in less time. Conversely, those patients with obstructive airways disease will take longer, sometimes up to 3 min.
3. The background flow during calibration should equal flow during the test. This is achieved by calibrating the system using the same set-up which will be applied to the patient. This technique has been shown to be very accurate and highly reproducible. Measurements of FRC by  $N_2$  washout on spontaneously breathing subjects are highly reproducible, with a COV for repeated measurements of <7.1% [40].

4. The resolution and, thus, the accuracy of the N<sub>2</sub> washout method depends on the level of the alveolar N<sub>2</sub> concentration before the test. When the patient is breathing gas with a relatively high fraction of inspired oxygen (F<sub>I,O<sub>2</sub></sub>) (relatively low F<sub>I,N<sub>2</sub></sub>), the volume of N<sub>2</sub> to be washed out is much smaller, which may affect the results. It follows that, when the patient is on a very high F<sub>I,O<sub>2</sub></sub> (70–100% O<sub>2</sub>), usually as a result of restrictive disease (e.g. adult respiratory distress syndrome (ARDS)) with small lung volumes, the technique cannot be used at all because there is virtually no N<sub>2</sub> to wash out.

In order to avoid concentrations of even 50–70% O<sub>2</sub> in premature infants, a nonrespiratory gas, such as helium, can be mixed with the inspired oxygen.

GEUBELLE *et al.* [42] using the helium dilution technique, showed that breathing 100% O<sub>2</sub> decreased lung volume in infants. This fits with the theory that FRC values measured at high F<sub>I,O<sub>2</sub></sub> should be smaller than those measured at F<sub>I,O<sub>2</sub></sub> = 0.21, as a result of a decrease in lung volume from the loss of "nitrogen-splinting" when 100% O<sub>2</sub> is used. It follows, in theory, that the breathing of 100% O<sub>2</sub> for short periods during repeated N<sub>2</sub> washout manoeuvres could cause a systematic decrease in the FRC recorded by this technique. This has not yet been reported.

5. The technique is also unsuitable for ventilated infants and children, because there is no way to assure constant gas flow in this situation, and the flow during calibration differs from that during the test because the compliance of the tubing of the ventilator and the calibration apparatus differs from that of the patient's respiratory system.

### FRC measurement during mechanical ventilation

#### Helium (He) dilution

The closed-circuit He dilution has been adapted by HELDT *et al.* [43] to measure FRC of ventilated adults, and, in a technically more difficult exercise, of ventilated infants. Unfortunately, the method adds compliance to the ventilation circuit, the complex switching valves and rebreathing systems add resistance, and O<sub>2</sub> consumption may not be perfectly balanced by O<sub>2</sub> supply, leading to errors in the measurement. The initial concentration of He in the circuit can range between 6 and 15%, although concentrations as low as 3% have been used. This means that the helium dilution method has the advantage of application to patients with severe lung disease requiring markedly elevated inspired oxygen concentrations (F<sub>I,O<sub>2</sub></sub> < 0.97) compared with N<sub>2</sub> washout (F<sub>I,O<sub>2</sub></sub> < 0.70). However, particularly in infants, the technique is not widely used for clinical purposes during mechanical ventilation.

#### Sulphur hexafluoride (SF<sub>6</sub>) washout

This method was first described in 1985 [44] in adults. It is an open circuit tracer gas washout, employing a device for dispensing SF<sub>6</sub> into the inspiratory limb of the ventilator circuit, a fast SF<sub>6</sub> analyser, a pneumotachograph and a computer. The dispensing device delivers SF<sub>6</sub> into the airway in proportion to inspiratory flow, so that the inspired SF<sub>6</sub> is held constant, usually at about 0.5%. The COV in mechanically ventilated adults is

< 6.6% [11]. The technique has since been applied to spontaneously breathing adults and infants, as well as those receiving mechanical ventilation [11–14].

#### Nitrogen (N<sub>2</sub>) washout

The technique which can be used at the bedside most easily during mechanical ventilation is the nitrogen washout method.

1. In 1981, PALOSKI *et al.* [45] developed a technique for measurement of FRC of critically ill adults during mechanical ventilation. They used a second ventilator with a high F<sub>I,O<sub>2</sub></sub> to wash out the N<sub>2</sub>. By using a system that was able to sample N<sub>2</sub> and measure instantaneous flow at a rate of 30 samples·s<sup>-1</sup>, they integrated these two variables breath-by-breath to obtain the total of washed out N<sub>2</sub> after summation of all breaths. Their system was very cumbersome, and was applicable only to adults in laboratory conditions.

2. In 1980, RICHARDSON and co-workers [46] developed a system capable of measuring FRC during mechanical ventilation, based on a mathematical model that estimated FRC from the end-tidal N<sub>2</sub> concentration of the first four breaths of the washout procedure. The device assumed a one-space lung model and an even distribution of ventilation in the subjects; two assumptions that are not always met, because slowly ventilated lung regions are expected to exist in many infants and children ventilated for respiratory failure. This caused underestimation of FRC in patients with different time constants at different lung regions. The system was not automated and the signals were recorded on plotters requiring hand integration and planimetry for final calculations, which introduced inaccuracies to the method. Moreover, alveolar ventilation was determined from the average tidal volume and respiratory rate of these first four breaths. The system also required quite cumbersome calibration before each set of tests. In 1982, RICHARDSON and co-workers [47] developed the technique further by incorporating a PC, which improved the accuracy and the speed of obtaining the results, but did not solve the other problems. However, they were later able to use the system in preterm infants with respiratory distress syndrome (RDS) [48].

3. The technique developed by GERHARDT *et al.* [40] is not immediately applicable to ventilated children, mainly because the gas flow during calibration does not equal the flow during the test. In order to overcome this difficulty, SIVAN *et al.* [41] used the respiratory mass spectrometer already "in-line" for measuring the instantaneous N<sub>2</sub> concentration, to record the minute ventilation (V<sub>E</sub>) by the argon dilution technique [49]. At FRC, the patient is switched to a second ventilator delivering 100% O<sub>2</sub> (washout ventilator) and washout starts. The equations for measuring N<sub>2</sub> volume hold both for calibration and test procedures:

$$VN_{2\text{cal}} = V'_{\text{cal}} \int [N_2]_{\text{cal}} \cdot dt \quad (9)$$

$$VN_{2\text{test}} = V'_{\text{test}} \int [N_2]_{\text{test}} \cdot dt \quad (10)$$

Dividing Equation 9 by Equation 10:

$$VN_{2\text{test}} = \frac{V'_{\text{test}}}{V'_{\text{cal}}} \cdot \frac{VN_{2\text{cal}}}{\int [N_2]_{\text{cal}} \cdot dt} \cdot \int [N_2]_{\text{test}} \cdot dt \quad (11)$$

The ratio  $V'_{\text{test}}/V'_{\text{cal}}$  is obtained from the minute ventilations measured by the argon dilution technique (utilizing a respiratory mass spectrometer) during the calibration and the study (test):

$$\frac{V'_{\text{test}}}{V'_{\text{cal}}} = \frac{V'_{\text{E,test}}}{V'_{\text{E,cal}}}$$

and the final equation is:

$$VN_{2\text{test}} = \frac{V'_{\text{E,test}}}{V'_{\text{E,cal}}} \cdot \frac{VN_{2\text{cal}}}{\int [N_2]_{\text{cal}} \cdot dt} \cdot \int [N_2]_{\text{test}} \cdot dt$$

$V'_{\text{E,test}}$  and  $V'_{\text{E,cal}}$ , are obtained by the argon dilution technique: the ratio  $VN_{2\text{cal}}/\int [N_2]_{\text{cal}} \cdot dt$  is defined during the calibration procedure. Hence, the FRC can be directly calculated from the integrated  $N_2$  concentration.

The technique has been shown to be accurate and reproducible. The COV is <6.5% [41].

The method can also be applied to the determination of elevated lung volumes [50], including TLC [51], although the presence of obstructed airways will cause greater error in infants and young children.

#### *Procedure for testing*

The experimental system consists of a second ventilator that delivers 100%  $O_2$  (washout ventilator) and has the same settings as the patient's ventilator.

Both ventilators are connected to the proximal end of the ETT through a slider valve, which is activated at FRC, when the patient is switched to the washout ventilator. The gas leaving that ventilator *via* the exhalation port is routed through a mixing chamber, and the  $N_2$  concentration is then analysed continuously by respiratory mass spectrometer, which also measures the  $V'_{\text{E}}$  by the argon dilution technique [49]. The mixing chamber must meet design needs for measurements of  $O_2$  consumption and for flow measurement by the argon dilution technique, and, therefore, meet the criteria for effective mixing. It should contain at least three serial channels that include baffles and vanes that recirculate air from the latter back to a previous channel before exiting past the sampling port. This greatly enhances mixing and provides a rapid equilibration within the chamber. The chamber size should be no less than 600 mL for ventilated infants and young children. A PC-based signal processing unit in line with the mass spectrometer integrates the  $N_2$  concentration signal electronically and provides a real-time display of the  $N_2$  concentration ( $N_2$  washout curve), and the integrated  $N_2$  concentration units on the monitor. SensorMedics (Model 2600 Pediatric Pulmonary Unit; Anaheim, CA, USA) provides a commercial system which will also control the slider valve and will automatically calculate the FRC at the end of the washout period, according to the  $V'_{\text{E}}$  and the patient's alveolar  $N_2$  concentration measured before the study. The criteria for the completion of the washout curve are: that the nitrogen concentration on the mass spectrometer readout is stable at zero; and that the  $N_2$  washout curve on the screen is back to baseline (zero). The length of time taken to wash out the  $N_2$  from the

lungs should be recorded for each study of the subject, as should the values of  $N_2$  washed out both from the high and low volume points of the two-point calibration method. Nitrogen integration should be performed at a minimum of 25 samples·s<sup>-1</sup>. This sampling rate is well in excess of the rate of change of the mixed  $N_2$  signal, and should ensure that no data are lost.

The accuracy of the argon dilution technique is within  $\pm 5\%$  when compared with Douglas bag collection [49]. The accuracy of the respiratory mass spectrometer is: resolution up to one mass unit; stability, better than 1% over 24 h; linearity, better than 1% over calibrated range; detection, down to 10 parts per million (ppm). It should be noted that, in this technique, the absolute values of each flow (flow during washout and during calibration) are not very important because the absolute values are not used for FRC determination, and the correction factor is based on their ratio only. Thus, even if the flow measurement is off by a certain percentage, this cancels itself as long as the flow measurement is constant over time. This means that the factors that determine the accuracy are the variability and the linearity of the mass spectrometer, both better than 1%.

Two types of ventilators have been formally tested [41]: 1) a continuous flow (pressure mode) ventilator (IV-100-B; Sechrist, Anaheim, CA, USA); and 2) an intermittent flow ventilator (servo-controlled Siemens Servo 900C; Solna, Sweden) in pressure and volume modes. Whenever the continuous flow on the Sechrist ventilator was relatively high with respect to the absolute amount of  $N_2$  washed out (resulting from low patient  $V'_{\text{E}}$ , high patient  $F_{\text{I},O_2}$  or very low FRC), the  $N_2$  concentration signal was very small, because a small amount of  $N_2$  was being mixed with a large amount of washout gas. In that situation, a "splitter isolation valve" (e.g. model No. 8890; Boehringer Laboratories, Wyndwood, PA, USA) was placed at the end of the ETT, which directed only the gas exhaled from the patient to the mixing chamber. The resistance of the valve was >1 cmH<sub>2</sub>O at 10 L·min<sup>-1</sup> and the dead space was 3 mL. When the splitter valve was used, the ventilator positive-end expiratory pressure (PEEP) was set to zero, and PEEP was controlled by a PEEP valve attached to the outlet of the splitter valve. Before connecting the PEEP valves, they were tested against a manometer for the range 0–20 cmH<sub>2</sub>O. In all situations where the gas reaching the mixing chamber was intermittent rather than continuous, a background flow of 100% oxygen (2–4 L·min<sup>-1</sup>) was added to the exhalation port to continuously drive the washed out gas to the mixing chamber [41].

$N_2$  washout is generally quicker than He dilution, rarely taking more than a minute in those with normal airways and breathing spontaneously, and rarely more than 3 min even with obstructed airways. By contrast, He dilution can take from 15 s to 5 min to complete.

#### *Assumptions and limitations*

1. The method requires an expensive respiratory mass spectrometer (except in the special circumstance noted above).
2. The method requires a second ventilator.
3. Like the method employed in nonventilated patients, it cannot be used in patients who are on very high

inspired O<sub>2</sub> concentrations. In practice, the system has been shown to be applicable to ventilated infants and children with  $F_{I,O_2} < 0.70$ .

4. When the patient is ventilated with a constant flow ventilator (time-cycled, pressure-preset), the washed out N<sub>2</sub> is diluted in a very large volume of gas, resulting in very low concentrations of N<sub>2</sub>, which may decrease the accuracy. This is especially true in small infants with lung disease on relatively high  $F_{I,O_2}$ , whose lung volume (and hence lung N<sub>2</sub> concentration) may be very small. A method by which this problem can be overcome is to use the splitter isolation valve (see above), which directs only exhaled gas to the mixing chamber. As an alternative, in all situations, it is technically much easier to use an intermittent flow ventilator with settings matched to the patient's ventilator of the same type, along with the patient in volume-controlled ventilation mode. The "calibration" ventilator is calibrated at the same  $V'_E$  delivered to the patient, and since the "calibration" and "test" (patient)  $V'_E$  are the same, there is no need to apply the ratio mathematics. Thus, the PC-based system calculates the FRC directly under these conditions, and the argon dilution technique is not needed since the ratio is equal to 1.

5. It is necessary to make sure that no gas containing N<sub>2</sub> leaks from the system. In most cases, there is a need for a cuffed ETT with mechanical ventilation. This can be a problem in ventilated infants and children who are traditionally ventilated with uncuffed tubes. In this situation, pharyngeal packing or gentle laryngeal pressure can be used to ensure no air leak is present. Alternatively, it has been shown that modern cuffed ETTs, carefully selected for size, are safe to use in this age group [52]. A bronchopulmonary fistula also constitutes a leak, and the FRC measurement should not be attempted under this condition.

6. Breathing 100% O<sub>2</sub> repeatedly for such tests may have toxic effects on preterm infants. This can be modified by using Heliox (helium and oxygen) gas mixtures. In this case, if a respiratory mass spectrometer is used for gas analysis, it must also be calibrated for helium.

7. The technique is time-consuming because repeated measurements are necessary, and both the argon dilution [49] and N<sub>2</sub> washout [41] systems must be independently calibrated.

8. Unlike the He dilution method, the N<sub>2</sub> washout method may also wash out blood and tissue N<sub>2</sub>. However, unlike the original descriptions for adults, where a 7 min period of O<sub>2</sub> breathing was calculated to wash out 220 mL of tissue nitrogen (up to 10% of the FRC) [24, 25], it has been suggested in newborn infants that the volume of tissue and blood N<sub>2</sub> washed out in a test is not more than 1% of the total [40]. That is, no significant amount of N<sub>2</sub> is washed out during a test which ends within 2–3 min at most, and at most will cause a 5% error [39, 53].

9. As with the integration technique of GERHARDT and co-workers [40, 53] for spontaneously breathing infants, the background flow must be extremely constant. Flow and volume are inversely related, so that an increase in flow of 10% will decrease the N<sub>2</sub> volume recorded by approximately the same amount, and thus the FRC measured.

### *Equipment and technical procedures*

One of the major difficulties in comparing and interpreting results from different centres is the lack of standardized equipment. Most equipment for measuring lung volumes on ventilators, especially in infants and young children, is "home-made", and necessary specifications for comparative conclusions are rarely presented in published manuscripts.

1. Major differences currently exist with respect to the thermal and frequency characteristics of the equipment, response time of gas analysers and the dead space and resistance of the apparatus. It is generally acknowledged that frequency response of measuring equipment should be adequate to record at least five times the basic frequency of respiratory manoeuvres being measured (*i.e.* at least 10 Hz for infant measurements). However, a standardized approach to simple, accurate methods of assessing frequency response of infant lung function equipment has yet to be defined [54]

2. Over the past few years, efforts have been made to introduce some degree of standardization into measurement techniques [20, 21, 55, 56], but criteria for technically satisfactory data have not been established clearly enough for recommendations to gain widespread acceptance. The establishment of a stable end-expiratory level prior to lung volume measurements (of FRC) has been recommended as a means of reducing intrasubject variability, but cannot be achieved unless time-based recordings of tidal breathing are available prior to the manoeuvres. The introduction of reliable automated systems to switch in the gas dilution method exactly at end-expiration has helped to reduce operator error considerably. Pneumotachographs, thermistors or mass flow sensors can be used to determine the end expiratory level (EEL), but respiratory inductance or impedance recordings, or end-tidal CO<sub>2</sub> measurements are unsuitable for the task because of phase lags between that which they record and actual movement of gas in the airway.

3. Methods of overcoming the potential practical and theoretical difficulties encountered in the N<sub>2</sub> washout technique have only recently been described [40, 41], and numerous methodological variations still exist between different centres employing this technique. Further work is required before a standardized approach can be adopted.

4. There is a particular controversy concerning the N<sub>2</sub> washout technique, because the reported values of FRC obtained using this method in healthy infants, whilst similar to helium dilution values in infants and older children [17, 40, 57], are considerably lower than reported with body plethysmography in infants. Measurements in normal spontaneously breathing newborn infants show that FRC measured by body-box (32–38 mL·kg<sup>-1</sup>) is significantly higher than the FRC measured by N<sub>2</sub> washout (16–19 mL·kg<sup>-1</sup> with a regression to weight of 20.0 mL·kg<sup>-1</sup>) [53]. The differences may be due to several factors, such as: trapped gas not measured by the gas dilution techniques; unreliability of the plethysmographic methods in small infants because of airway closure; and technical difficulties with both the gas dilution methods.

5. With all techniques, there is controversy regarding how many measurements should be made in each patient, and the way in which results should be expressed.



Whereas it is relatively simple and quick to obtain 3–5 repeat measurements of  $FRC_{pleth}$ , this is less feasible with gas dilution techniques, due not only to the duration of rebreathing or washout required but also to the necessary interval between tests. Results based on a single recording are unlikely to be reliable. The absolute minimum for an acceptable result is probably the mean of two measurements within 10% of each other, although greater confidence would be obtained if three such measurements were available. For infants and children, in our laboratory, we normally perform three tests and accept the mean of the data if the spread is within 2 mL·kg<sup>-1</sup> body weight, *e.g.* a 10 kg infant has a predicted FRC of 204 mL, we accept the mean value if the range is within 20 mL.

6. GEUBELLE *et al.* [42] showed that breathing 100% O<sub>2</sub> affects lung volume in infants. This fits with the theory that FRC values measured at high  $F_{I,O_2}$  should be smaller than those measured at  $F_{I,O_2} = 0.21$ , as a result of a decrease in lung volume when 100% O<sub>2</sub> is used. This argument may hold for the He dilution technique only, because: a) it takes longer for equilibration to occur (especially in spontaneous breathing; b) the helium dilution technique can be applied at much greater  $F_{I,O_2}$  than the N<sub>2</sub> washout method; and c) the volume measured by the N<sub>2</sub> has been displaced and replaced.

In adults it has been proposed that breathing pure O<sub>2</sub> for about 3 min has little effect on FRC. Support for this view is provided by data from IBÁÑEZ *et al.* [58] both on spontaneously breathing subjects and mechanically ventilated patients, using the N<sub>2</sub> washout method. Conversely, other workers have not confirmed these findings in adult studies [59, 60], but have found results similar to GEUBELLE *et al.* [42].

7. Since flow and volume are inversely related, the background gas flow in the open nitrogen washout system must be very constant both for spontaneously breathing and mechanically ventilated patients (see above).

#### Normal values: spontaneous breathing

In 1986, GERHARDT *et al.* [61] reported normal values by the N<sub>2</sub> washout technique for children up to 5 yrs of age. The study sample was 50 children, with 14 less than 1 month of age. The weight ranged 1.2–26 kg, but the 95% confidence interval (95% CI) was rather large beyond 2 yrs of age, which may represent normal distribution but probably resulted from the small sample size for this age group (FRC·kg<sup>-1</sup> and FRC·cm<sup>-1</sup> were dependent on weight and length, respectively). Their regression equation for  $FRC_{N_2}$  yields predicted values (18–22 mL·kg<sup>-1</sup>) lower than those previously reported for helium dilution. However, more recently, TEPPER and ASDELL [17] measured both  $FRC_{He}$  and  $FRC_{N_2}$  in eight normal infants and found no difference between the results with the two methods, and the results were within the range previously reported as normal for the N<sub>2</sub> washout technique (mean  $FRC_{He} = 22.2$  mL·kg<sup>-1</sup>,  $FRC_{N_2} = 21.4$  mL·kg<sup>-1</sup>).

#### Normal values: mechanically assisted breathing

Controversy exists over the definition of "normal lungs" during mechanical ventilation. Factors that must

also be considered (especially in ventilated patients) when trying to establish normal values are the potential FRC-lowering effects of sedation and anaesthesia. Anaesthesia with a volatile gas, such as halothane has been reported to reduce lung volume markedly in all age groups [62], although ketamine does not [63]. Sedation with chloral hydrate makes no significant difference to FRC [18]. In children, when the patient is tested in the supine position whilst the normal data have been reported in the sitting position, a 25–30% downward adjustment of the predicted value should be made [64, 65]. However, this adjustment may not apply to sick, ventilated infants, smaller children and adults.

Patients who have their lung volumes determined whilst mechanically ventilated have an ETT in place, which bypasses the volume of the nasopharyngeal area. This volume has been measured postmortem in adults [66] and whilst dependent to a degree on head position, the volume represents approximately 50% of the anatomical dead space, *i.e.* 1 mL·kg<sup>-1</sup>. The infant's head is relatively much larger in proportion to body size than the adult's, and the relative contribution to total dead space in children is higher, up to 2.1 mL·kg<sup>-1</sup> in young infants [67]. Thus, "normal" FRC of mechanically ventilated patients will be lower than their spontaneously breathing counterparts, all other things being equal.

Therefore, true normal values for FRC for ventilated patients do not exist. SIVAN and co-workers [4] have published data on six children with normal lungs at the (usual) 2–4 cmH<sub>2</sub>O PEEP chosen by clinicians in these circumstances. Two children were close to the predicted values of GERHARDT *et al.* [61] (18–22 mL·kg<sup>-1</sup>; mean = 20.4 mL·kg<sup>-1</sup>) and the other four were 39–52% higher. They came back into the "normal" range only when PEEP was removed. On the other hand, HAMMER *et al.* [68] from the same laboratory, determined  $FRC_{N_2}$  in 10 ventilated infants with normal lungs as 24.4±1.7 mL·kg<sup>-1</sup>.

#### Direct comparison studies with other FRC techniques

There are, as yet, no published studies in small infants and young children which have compared the FRCs obtained by N<sub>2</sub> washout to the He dilution technique in the same mechanically ventilated patients.

DUBOIS *et al.* [29] showed close agreement between FRC measured by the plethysmographic technique and by the 7 min N<sub>2</sub> washout in normal subjects. YUKSEL *et al.* [69] compared  $FRC_{He}$  and  $FRC_{N_2}$  techniques in spontaneously breathing preterm and term infants recovering from pulmonary diseases, and found no difference between the two methods. TEPPER and ASDELL [17] compared the same two techniques in spontaneously breathing infants and young children. They reported only eight normal subjects, ranging in age from a few days to 31 months. They found no difference between the two methods (see above). KRAEMER *et al.* [57], in 54 older (7–16 yrs) healthy children, determined FRCs obtained by N<sub>2</sub> washout and He dilution, and also FRC by body plethysmography. There was no statistically significant difference in the lung volumes measured by any technique.

RICHARDSON and ANDERSON [47] used cats weighing approximately 2.7 kg to measure FRC both by N<sub>2</sub> washout and He dilution techniques in animals with normal

lungs (n=128), as well as those with pulmonary oedema (n=80) whilst being mechanically ventilated. FRC results by both methods in both studies were very close over the range 40–150 mL, with correlation coefficients of 0.921 and 0.989 (for normal cats and cats with pulmonary oedema, respectively), and slopes that were very close to the lines of identity. This proves that both gas dilution techniques are comparable and accurate, but it should be noted that these studies were performed under ideal conditions, *i.e.* animals sedated, paralysed and with breathing fully controlled by mechanical ventilation.

Similar comparative studies on mechanically ventilated adults (either under neuromuscular blockade or heavily sedated) also confirm that there is no significant difference between the two gas equilibration methods under these conditions [58, 70]. MITCHELL *et al.* [70], in 18 postcardiac surgery patients, found a correlation coefficient of 0.93, with a maximum difference of 430 mL between repeated trials. They also found a correlation coefficient of 0.97 in comparison studies in 21 ventilated patients with normal lungs, and a mean $\pm$ SD difference between paired measurements of 21 $\pm$ 213 mL. IBAÑEZ *et al.* [58], in dual studies performed on 12 mechanically ventilated patients with and without PEEP, found a correlation coefficient of 0.97 and no statistically significant difference between the two methods.

Hence, although reported results in infants and young children from studies that used the nitrogen washout method differ from those that used helium dilution, from the above direct comparison data it is reasonable to assume that most of the differences originate from environmental, methodological and technical problems and not from basic disagreements between the two gas equilibration techniques.

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