Measurement of Lung Volume by Sulfur Hexafluoride Washout during Spontaneous and Controlled Ventilation: Further Development of a Method

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An open circuit tracer gas washout method for measurement of lung volume in patients during anesthesia and intensive care is described and tested. The method employs a device for dispensing the tracer gas, sulfur hexafluoride (SF₆), a fast SF₆ analyzer, a pneumotachograph, and a computer. The dispensing device delivers SF₆ into the airway in proportion to instantaneous inspiratory flow so that inspiratory SF₆ concentration is held constant, usually at about 0.5%, regardless of the inspiratory flow pattern. The amount of SF₆ present in the lungs at the end of a washin is calculated during washout from signals representing expired SF₆ concentration and expired flow. From this, lung volume is derived. Accurate and reproducible results were obtained in lung model tests during ventilation with air, N₂O in O₂, and halothane in O₂. Functional residual capacity (FRC) was measured both with SF₆ washout and nitrogen washout in five mechanically ventilated patients. This gave the regression equation: $\text{FRC}_{\text{SF}_6} = 10 \text{ ml} + 1.01 \times \text{FRC}_{\text{N}_2}, r = 0.99$. A similar close agreement was observed for total lung capacity (TLC) and residual volume (RV) measurements in eight healthy, spontaneously breathing subjects: $\text{TLC}_{\text{SF}_6} = 91 \text{ ml} + 1.01 \times \text{TLC}_{\text{N}_2}, r = 0.99; \text{RV}_{\text{SF}_6} = -32 \text{ ml} + 0.97 \times \text{RV}_{\text{N}_2}, r = 0.95$. Comparison with body plethysmography in eight healthy, sitting subjects gave the regression equation: $\text{FRC}_{\text{SF}_6} = 180 \text{ ml} + 0.96 \times \text{FRC}_{\text{N}_2}, r = 0.99$. The median (range) for the coefficient of variation at duplicate determinations in 10 anesthetized, paralyzed, and mechanically ventilated adults was 3.0% (0.2–6.6%). The corresponding figures for seven spontaneously breathing and seven manually ventilated, anesthetized children were 2.8% (0–7.6%) and 0.6% (0.2–1.9%), respectively. It is concluded that the method can be used during both spontaneous breathing and controlled ventilation. (Key words: Lung functional residual capacity. Measurement technique: flow proportional admixture; sulfur hexafluoride washout.)

AN OPEN CIRCUIT tracer gas washout method for measurement of lung volume in mechanically ventilated patients has been described by Jonmarker et al. During washin, the tracer gas, sulfur hexafluoride (SF₆), is supplied via a magnetic valve, which opens during inspiration, and a thin catheter which ends in the airway close to the tracheal tube. FRC is calculated by a computer from signals representing expired SF₆ concentration and expiratory flow. The method has certain advantages: a low concentration of tracer gas can be used, washout is started simply by shutting the magnetic valve, no mixing chambers or bags for expired gas are needed, the process is automated so that the result is presented directly after washout, and the technique can be used during anesthesia with nitrous oxide and halothane. Since SF₆ has low solubility in body tissues, the method is theoretically applicable in patients with long equilibration periods. However, the tracer gas is delivered at a constant rate during inspiration. Insufflation patterns other than constant flow would, therefore, yield a varying inspiratory concentration of tracer gas and a resulting uneven distribution of SF₆ in nonhomogeneously ventilated lungs. This paper describes and evaluates a modified system that can be used with all patterns of inspiratory flow.

Materials and Methods

SYSTEM DESCRIPTION

The measurement system (fig. 1) includes a tracer gas dispensing unit, a heated Fleisch pneumotachograph (Gould) with a differential pressure transducer (CD 225-C or MP 45-1-871, Valdylane), an infrared SF₆ analyzer with the transducer placed over a cuvette in the airway, and a computer (PDP 11/23, Digital Equipment).

The tracer gas dispensing unit contains a piezoelectric valve (type PWAA 8000120H, Lee) which delivers tracer gas in short pulses. A microprocessor (type 4680, Satco) modulates the pulse frequency of the valve in proportion to flow, and the admixture of tracer gas can

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be kept at a constant level irrespective of the inspiratory flow pattern. The lung volume measurement requires that there is no rebreathing. This limitation also entails the advantage that zero-adjustment of the SF₆ analyzer can be done during each inspiration. This is accomplished by the microprocessor, which is programmed to initiate a reset of the zero level when SF₆ free gas has passed through the analyzer for at least 0.5 s (adults) or 0.2 s (children). The pneumotachograph is heated to ensure thermal stability and to avoid condensation in the capillaries. For the same reason, and also in order to trap mucus, a small heat-moisture-exchanger (Humidivent®, Gibeck, Sweden) is usually placed between the pneumotachograph and the patient.

The measuring procedure and the computations are similar to those described by Jonmarker et al.⁴: SF₆ is washed in until a stable and uniform alveolar concentration of approximately 0.5% is reached. At the end of washin, the alveolar SF₆ concentration is obtained as the mean concentration during expiration of the second half of the tidal volume. The mean of the last five breaths of washin is used. Washout is started simply by stopping tracer gas infusion between two inspirations, and is considered complete when the mean expired SF₆ concentration in the last five breaths is less than 0.001%. During the washout period, instantaneous expiratory SF₆ flow is calculated by the computer which multiplies expiratory flow and SF₆ concentration every 10 ms. The total volume of washed-out SF₆ is obtained by integration. FRC is calculated as the volume of SF₆ washed-out divided by the alveolar concentration at the end of washin. The obtained value is converted to BTPS conditions and the apparatus dead space is subtracted. The result is displayed on the computer-screen immediately after washout.

**Calibrations.** The SF₆ analyzer was calibrated with a precision gas mixture containing 0.50 ± 0.01% SF₆ (Alfax, Sweden). Since the analyzer is quite stable,⁵ daily calibrations were not done. The linearity of the SF₆ concentration reading was ascertained as described previously.⁵ The airway flow signal was calibrated with a 1-liter syringe or accurate reciprocal pumps (485 ml or 30 ml) and the relevant gas mixture. Zero adjustment of the flow signal was done before each FRC determination. Adjustment of the zero level was repeated if it had changed by more than 1 ml/s. A factor of 1.09 was used to convert FRC and flow from ATPS to BTPS conditions.

**Evaluation of the Measurement System**

All tests in humans were approved by the local Human Investigations Committee, and informed consent was obtained from the participants or their guardians.

**Tracer gas flow as a function of inspiratory flow.** To measure the amount of tracer gas dispensed during different inspiratory flow rates, the SF₆ dispensing valve (fig. 1) was disconnected from the measurement system and attached to a piece of tubing which had its distal end placed under a water seal in a graduated glass cylinder. The pneumotachograph (Fleisch no 1) and the rest of the measurement system was connected to a lung model and ventilated with air by a ventilator (Servo® 900C, Siemens-Elema) set to deliver a constant inspiratory flow at a rate of 10 breaths/min. To obtain a wide range of inspiratory flows, the tidal volume was varied from 300–1500 ml, and the insufflation time from 25–67% of the breathing cycle. The SF₆ volume dispensed by the unit during 10 consecutive breaths was recorded so that the flow could be calculated.

**Tracer gas flow and inspired tracer gas concentration during different inspiratory flow patterns.** A similar set-up was used to assess the tracer gas flow during different inspiratory flow patterns. The tracer gas flow was obtained by measuring the pressure drop across a resistance, using a differential pressure transducer (MP 45-1-871, Validyne). The ventilator was used to give three different inspiratory flow patterns: square-wave, accelerating, and decelerating flow. A more irregular flow pattern was created by breathing through the pneumotachograph. The inspiratory flow signal and the SF₆ flow signal were recorded on an ink jet recorder (Mingograph® 81, Siemens-Elema).

These flow patterns were also used to test whether the SF₆ infused by the dispensing unit gave a uniform tracer gas concentration in the inspire. During this test, the SF₆ transducer was placed between the tracer gas dispensing unit and the lung model. The inspiratory...
SF₆ concentration and the inspiratory flow were recorded.

FRC measurements in lung models. One lung model consisted of a bottle into which two tubes were inserted (fig. 2A). One of the tubes was connected to the measurement system and the other to a syringe. The model was ventilated with air by moving the plunger of the syringe with a tidal volume of 60 ml at a rate of about 20/min. FRC of the model was varied between 30 and 1000 ml. A larger model, a U-shaped vessel (fig. 2B), one limb of which was connected to the measurement system, was ventilated with air by a ventilator while FRC was varied between 500 and 4000 ml. Three ventilatory settings were tested (fig. 2B). The inspiratory-expiratory ratio was 1/1. Fleish pneumotachographs no 0 and 2 were used in the small and large model lung measurements, respectively.

To test the influence of anesthetic gases on FRC measurements, the large lung model was ventilated with air, 50% N₂O in O₂, and 1% halothane in O₂ by a ventilator (Servo® 900C) set at 20 breaths/min, a decelerating flow, and a tidal volume of 800 ml. Peak airway pressure was 20 cm H₂O. Inspiratory-expiratory ratio was 1/1.

Comparison with body plethysmography. Simultaneous SF₆ washout and body plethysmographic measurements were made in eight healthy, sitting, spontaneously breathing subjects (10–89 yr of age). The inspiratory and expiratory limb of the breathing tubing, as well as cables from the pneumotachograph (Fleisch no 2), the tracer gas dispensing valve, and the SF₆ transducer were passed via air-tight seals through the wall of the body plethysmograph. The FRC measurement system (fig. 1) was placed between the subject and the Y-piece of the tubing. A shutter was placed in the apparatus dead space close to the mouth. The test subject was comfortably seated in the body box and equipped with a nose-clip. When a stable alveolar SF₆ concentration of about 0.5% was reached, the shutter was closed and SF₆ delivery was stopped. The subject was asked to make breathing efforts against the closed shutter at a frequency of 1 Hz or less to allow the thoracic gas volume to be assessed. After these maneuvers, the shutter was opened and SF₆ washout commenced. Thus, both measurements refer to the same moment.

Comparison with nitrogen washout. Eight healthy sitting subjects, 10–43 yr of age, were studied. The readout of the nitrogen analyzer (model 720, Ohio Medical products) was affected by SF₆, so that simultaneous measurements with both methods were not possible. The subjects were studied at total lung capacity (TLC) and at residual volume (RV), because these volumes were easier for the subjects to reproduce than was FRC. N₂ washout measurement of TLC was done as follows. The subject, equipped with a nose-clip, breathed air through a mouthpiece. After a maximal inspiration, he/she expired into a Douglas bag, and washout into the bag continued during oxygen breathing until an end-tidal N₂ concentration of approximately 2% was reached. RV was measured in a similar manner, except that
washout was started after a maximal expiration. After the maximal initial inspiration and expiration, respectively, the subject breathed oxygen at FRC, except for the last breath during washout, when a maximal expiration was made. The amount of N₂ collected in the bag and the expired concentration before and at the end of washout were used to calculate the lung volume.⁴,⁷ The N₂ concentration in the airway and in the bag were measured with the nitrogen analyzer. Similar breathing maneuvers were done before SF₆ washout. The measurements were made in duplicate, so that 2 × 2 TLC and 2 × 2 RV determinations were done in each subject.

To test the system during mechanical ventilation, five patients, 37–71 yr of age, were studied after cardiac surgery. The patients were sedated, paralyzed, and ventilated with 50% O₂ in N₂ by pressure-controlled ventilation, i.e., decelerating inspiratory flow. Four patients had no history of lung disease, and one patient had moderate chronic obstructive lung disease. Each patient was examined without and with 5–8 cm H₂O of positive end-expiratory pressure (PEEP). N₂ and SF₆ washout measurements of lung volume were performed sequentially with a set-up using two synchronized ventilators.¹ The measurements were performed in duplicate to allow assessment of reproducibility.

Reproducibility in anesthetized patients. Duplicate determinations were also done in ten anesthetized and paralyzed adults, non-smokers and without lung disease, who were mechanically ventilated with 70% N₂O in O₂, in seven anesthetized children, 3–8 yr of age, breathing 1% halothane and 50–65% N₂O in O₂ through an endotracheal tube; and in seven anesthetized and paralyzed children, 3 months–7 yr of age, who were manually ventilated with a similar gas mixture or with 1% halothane in air–O₂. The result was expressed as the coefficient of variation, i.e., as SD/m (D/m × √2, where D is the absolute value of the difference between two observations and m the mean).

Statistics. Regression lines were obtained by the method of least squares. The residual standard deviation (RSD) around the regression line was calculated. Student’s two-sided t test was used for assessment of significance. The t test for paired data was used in experiments in which the difference between SF₆ washout and a reference method was assessed. Two-way analysis of variance (ANOVA) was used to assess the effects of different patterns of ventilation and gas mixtures on FRC measurements. P values below 0.05 were considered to indicate significance. The data are given as mean ± 1 SD when not otherwise indicated.

Results

Tracer Gas Flow as a Function of Inspiratory Flow

The regression equation was: SF₆ flow = 0.14 ml/s + 0.0048 × inspiratory flow, r = 0.999, RSD = 0.05 ml/s. The intercept was significantly different from zero (P < 0.001).

Tracer Gas Flow and Inspired Tracer Gas Concentration during Different Inspiratory Flow Patterns

Although the SF₆ flow signal was somewhat distorted, there was a close similarity between the two flow signals (fig. 3). Figure 4 shows the resulting inspiratory SF₆ concentration. The inspirate contained a uniform SF₆ concentration for all tested inspiratory flow patterns.

FRC Measurements in Lung Models

The results for the small model lung are shown in figure 2A. Each point represents a single determina-
FRC MEASUREMENT BY SF₆ WASHOUT

Comparison with Body Plethysmography

The result is shown in figure 5. The difference between the lung volume measurements by SF₆ washout and by body plethysmography was 49 ± 197 ml (NS). The regression equation was: FRC_{SF₆} = 180 ml + 0.96 × FRC_{box}, r = 0.99, RSD = 198 ml. The slope and intercept were not significantly different from 1.0 and zero, respectively.

Comparison with Nitrogen Washout

The difference between residual volume (RV) measurement by SF₆ washout and N₂ washout in healthy subjects (fig. 6A) was −64 ± 143 ml (NS). The corresponding difference for total lung capacity (TLC) was 119 ± 200 ml (NS). The regression equations were RV_{SF₆} = −32 ml + 0.97 × RV_{N₂}, r = 0.95; and TLC_{SF₆} = 91 ml + 1.01 × TLC_{N₂}, r = 0.99. The regression equation for the total material was: lung volume_{SF₆} = 91 ml + 1.03 × lung volume_{N₂}, r = 0.99, RSD = 183 ml. The slopes and intercepts were not significantly different from 1.0 and zero, respectively. The difference between FRC obtained by SF₆ washout and N₂ washout in five mechanically ventilated patients (fig. 6B) was 81 ± 98 ml (NS) without, and 60 ± 60 ml (NS) with PEEP. The median coefficient of variation during ventilation with and without PEEP was 3.1% (range 0.8–4.9%) for the FRC values obtained by SF₆ washout, and 0.8% (range 0.3–14.8%) for the FRC values obtained by N₂ washout. The regression equation was: FRC_{SF₆} = 10 ml + 1.04 × FRC_{N₂}, r = 0.99, RSD = 90 ml. The slope and intercept were not significantly different from 1.0 and zero, respectively. The time needed for N₂ washout to the 2% level and for SF₆ washout to 0.001% was 1.0 ± 0.5 min and 2.7 ± 1.6 min, respectively.

Fig. 4. Performance of the tracer gas dispensing unit. The SF₆ concentration (SF₆) is shown during four different patterns of inspiratory flow (V_{insp}). The flow patterns were generated as in figure 3. The SF₆ signal does not return to zero during the subsequent “expiration.” This is due to reentry of SF₆-containing gas.

Reproducibility in Anesthetized Patients

In paralyzed and mechanically ventilated adults FRC ranged from 1.3 to 3.4 l. The median coefficient of

Table 1. Actual and Measured Volume (ml) of a Model Lung During Ventilation With Different Inspired Gas Compositions. Two Measurements (No 1 and 2) Were Made for Each Condition.

<table>
<thead>
<tr>
<th>Actual Volume, ml</th>
<th>Measured Volume, ml During Ventilation With Air</th>
<th>50% N₂O in O₂</th>
<th>1% Halothane in O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No 1</td>
<td>No 2</td>
<td>No 1</td>
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<td>561</td>
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variation was 3.0% (range 0.2–6.6%). In spontaneously breathing children, FRC varied between 314 and 699 ml. The median coefficient of variation was 2.8% (range 0.0–7.6%). In paralyzed and manually ventilated children FRC varied between 135 and 683 ml. The median coefficient of variation was 0.6% (range 0.2–1.9%).

Discussion

The tracer gas dispensing device is an important component of the measurement system. The device gave a uniform inspiratory SF₆ concentration for all the tested inspiratory flow patterns. The intercept in the regression equation between SF₆ flow and inspiratory flow indicates, however, that the device disperses SF₆ somewhat in excess at low inspiratory flows. This can probably be corrected, but we have not deemed this necessary, since the resulting error is small; if the unit is preset to deliver 0.5% SF₆ into the patient at an inspiratory flow of 500 ml/s, then actual concentration will be 0.49% at 1000 ml/s and 0.62% at 100 ml/s. The inspired gas is subjected to mixing in the airways and lungs, and transient fluctuations of inspired SF₆ concentration of this magnitude should not cause significant errors in FRC determinations. For children, we dilute the tracer gas so that the device works in its optimal range.

SF₆ delivery is not affected by airway pressure. Bench tests of the dispensing device show that the inspiratory SF₆ concentration remains unchanged when inspiratory pressure is varied between 0 and 70 mmHg. To prevent

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**Fig. 6.** Lung volumes obtained with nitrogen and SF₆ washout. The center of each cross is the mean of duplicate N₂-washout measurements versus the mean of duplicate SF₆-washout measurements. The bars indicate the range. The lines of identity are shown. Panel A: eight healthy awake subjects. Values above 3 l represent measured total lung capacity with the two methods and values below 3 l are residual lung volumes. Panel B: five mechanically ventilated patients recovering from cardiac surgery. Measurements were obtained during 5 or 8 cm H₂O of PEEP and during zero end-expiratory pressure. The numbers refer to individual patients.
streaming during the measurements of inspired SF₆ concentration (fig. 4), it was necessary to adjust the dimensions of the tubing in order to accomplish turbulence and good mixing. It was felt that this would mimic the events in patients. During ventilator treatment, turbulence will occur in the tracheal tube and its connector and during spontaneous breathing in the airway, especially in the larynx.⁸

In the previously described system,¹ only the expiratory component of airway flow was of interest. This was obtained with the expiratory flow meter of a Servo Ventilator, i.e., away from the patient. In the present system, a pneumotachograph was placed in the apparatus dead space to allow both inspiratory and expiratory flow to be measured. The proximity between the pneumotachograph and the airway has the drawback that secretions, humidity, and variation in temperature may affect the flow measurement. These problems can be minimized by using a heated pneumotachograph and by placing a small heat-moisture-exchanger between the airway opening and the flowmeter. The day-to-day change in flow calibration seldom exceeded 1%. However, a switch from air to oxygen causes a change of about 9%, so that it is important that calibration is done with the relevant gas mixture. Although 0.5% SF₆ in air should theoretically have a viscosity different from that of pure air, we could not detect such an effect in bench tests, which ought to have disclosed changes in flowmeter calibration exceeding 1%. Without a heat-moisture-exchanger, the present measurement system has an apparatus dead space of 8 ml if a Fleisch pneumotachograph no 00 is used and 45 ml with a no 1. Although the latter figure is acceptable in most adults, 8 ml may be too large in spontaneously breathing infants.

The properties of the SF₆ analyzer have been described previously.⁵ It has a rapid response with a lag time and rise time of about 2 and 10 ms, respectively,⁵ which obviates the need to compensate for delay time between the SF₆ concentration and airway flow signals.⁵ The signal obtained from the SF₆ analyzer used in the present study was not disturbed by N₂O, CO₂, or halothane. Enflurane and isoflurane caused significant interference; 2% enflurane and 2% isoflurane resulted in a reading corresponding to 0.008% and 0.009% SF₆, respectively. Since the analyzer is zero-adjusted during each inspiration, this disturbance will diminish when inspired and expired concentration approach each other. It should be possible to compensate for the remaining small disturbance by observing the signal before starting SF₆ washin. However, we have, as yet, not done any FRC measurements during enflurane or isoflurane anesthesia.

While sulfur hexafluoride is biologically inert and nontoxic, sulfur tetrafluoride (SF₄) and disulfur decafluoride (S₂F₁₀) are considered possible contaminants in commercially available SF₆.** To exclude the presence of these toxic impurities, each lot of gas should be chemically analyzed and biologically tested, e.g., by exposing mice to 80% SF₆ for 24 h. The purity of the gas we used was checked in this way by the manufacturer. In this connection, the high sensitivity of the analyzer is advantageous, as it makes it possible to use low alveolar SF₆ concentrations (0.5% or less). This should further increase the margin of safety.

The FRC measurements were accurate in lung models, and were not influenced by nitrous oxide or halothane. We found close correspondence between FRC measured by SF₆ washout and the thoracic gas volume measured by body plethysmography in healthy individuals. These results are consistent with previous studies in which gas dilution techniques have been compared with body plethysmography in healthy sitting individuals.¹⁰-¹² In patients with chronic obstructive lung disease, the relation would probably be different. Gas dilution methods would underestimate the lung volume due to lack of representation of poorly ventilated regions,¹¹ and body plethysmography would tend to overestimate the thoracic gas volume.¹²

A close agreement was also observed between SF₆ and N₂ washout measurement of lung volume. This was to be expected. With one exception, the patients and subjects were free from obstructive lung disease. Hence, washout periods were short, so that nitrogen evolved from body tissues could be estimated with reasonable accuracy. Furthermore, fast equilibrium of SF₆ in the lungs could be foreseen, in spite of its low diffusivity. The result agrees with previous findings in patients ventilated with a square wave flow.¹

We conclude that the present system retains the advantages of its predecessor, but has a wider scope. It can be used both during spontaneous breathing and during artificial ventilation in awake and anesthetized patients.

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References


