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A Novel Physiological Investigation of the Functional Residual Capacity by the Bias Flow Nitrogen Washout Technique in Infants

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Summary

The dynamic functional residual capacity (FRC_{dyn}), the lung volume most routinely measured in infants, is an unreliable volume landmark. In addition to the FRC_{dyn} , we measured the (passive) static FRC (FRC_{st}) by inducing a brief post-hyperventilation apnea (PHA) in 33 healthy infants aged 7.4–127.2 weeks. A commercial system for nitrogen (N_2) washout to measure FRC, and a custom made system to monitor and record flow and airway opening pressure signals in real-time were used in unison. Infants were manually hyperventilated to induce a PHA. After the last passive expiration, FRC_{st} was estimated by measuring the volume of N_2 expired after end-passive expiratory switching of the inspired gas from room air to 100% oxygen during the post-expiratory apneic pause. Repeatable intrasubject FRC_{st} and FRC_{dyn} measurements overlapped in most infants including the younger ones ($P = 0.2839$). Mean (95% confidence interval [CI]) FRC_{st} was 21.1 (20.0–22.3), and error-corrected FRC_{dyn} was 21.4 (20.4–22.4) ml/kg. Mean (washout time [t]) $tFRC_{st}$ was longer than $tFRC_{dyn}$ 60 sec (95% CI 55–65) versus 47 sec (95% CI 43–51) ($P < 0.0001$). The FRC and washout time were dependent on body length, weight and age. We conclude that the FRC_{st} is not different from the FRC_{dyn} in infants. The FRC_{st} is a reliable volume landmark because the PHA stabilizes the end-expiratory level by potentially abolishing the sedated infant's breathing strategies. The FRC_{st} lacks potential sources of errors and disadvantages associated with measuring the FRC_{dyn} . The findings cast significant doubt on the traditional physiology of air trapping in healthy infants' lungs.

Keywords

lung volume; infant or animal lung function; inert gas or nitrogen washout

INTRODUCTION

With normal tidal breathing in adults and older children, the normal end-expiratory lung volume, which is the static (FRC_{st}) or passive FRC, coincides with the elastic equilibrium volume (EEV) of the respiratory system where the outward recoil of the chest wall is balanced by the inward recoil of the lungs. The compliance of the chest wall is nearly threefold that of the lung in infancy, and becomes equal by 2 years of age as in adults.¹ Therefore, the balance of the elastic recoil forces of the lung and chest wall in the infant

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predicts a very low FRC of only 10% of the total lung capacity, which is incompatible with peripheral airways stability or adequate gas exchange.² Therefore, infants incorporate breathing strategies which include postinspiratory activity of the diaphragm, laryngeal narrowing during inspiration, and braking of expiration to maintain a dynamic FRC (FRC_{dyn}) above the passively determined level (FRC_{st}), and inspire before expiration ends passively.^{3–6} Hence, lungs and chest wall mechanics cause the infant to breathe at a higher rate, rather than increasing the tidal volume.^{7,8} The Hering–Breuer inflation reflex (HBIR) which is active in infants, can facilitate the rapid respiratory rate important for the maintenance of an adequate resting lung volume for gas exchange.^{4,7,9} The activity of the HBIR is maximal in early infancy, remains unchanged in the first 2 months of life, and declines to 50% at 1 year of age.^{10–13} Thus, the routine measurement of FRC in spontaneously breathing infants has always been a measurement of the FRC_{dyn} , and the variability in end-expiratory level (EEL) has impeded the assessment and interpretation of not only lung volumes but also respiratory mechanics, and forced expiratory flows within the tidal breathing range.^{14–18}

The aim of this study was to present the methodological aspects of a new technique for the multiple-breath nitrogen washout (MBNW) to measure the FRC_{st} in infants, and to compare the FRC_{st} with the FRC_{dyn} in a group of healthy infants. The underlying concept of this investigation was the induction of a brief post-hyperventilation apnea (PHA) or post-expiratory pause. Passive hyperventilation resulting in hypocapnea has long been known to cause a temporary inhibition of the respiratory drive.^{19–21} The phenomenon of a brief PHA has been adapted to perform raised volume forced expirations, and to measure the residual volume in infants.^{16,22,23} We hypothesized that the PHA would abolish the sedated infant's breathing strategies, and create after end-passive exhalation, a reliable volume landmark that was only determined by the EEV of the infant's respiratory system. Therefore, a reliable measurement of FRC_{st} would then be obtained by measuring the volume of nitrogen (N_2) expired after end passive expiratory switching of the inspired gas from room air to 100% oxygen before the resumption of spontaneous inspiration. Based on the known infant's breathing strategies to prevent airway closure, we also hypothesized that the mean intrasubject FRC_{dyn} would be higher than the FRC_{st} , especially in young infants.^{2–18}

MATERIALS AND METHODS

Subjects

Measurements were performed on 23 healthy Caucasian (11 boys) and 10 black (3 boys) infants and young children participating in a respiratory physiology study. Infants were recruited at Arkansas Children's Hospital in Little Rock, Arkansas. They were recruited from general pediatric clinics, the newborn nursery unit, from pediatricians within the city, and from advertisements.

Median (range) age was 27.1 (7.4–127.2) weeks, weight was 8.44 (5.03–13.80) kg and height was 70.3 (56.7–93.6) cm.

The study inclusion criteria were the following: (1) gestational age of at least 37 weeks and birthweight at least 2.5 kg, (2) no more than an incidental second hand cigarette smoke exposure, and (3) no history other than transient respiratory problems during the neonatal period of less than 24 hr duration with a fractional inspiratory oxygen concentration of less than 0.3. Infants were excluded from testing if they were clinically unstable, had a significant upper airway obstruction, an acute respiratory illness 3 weeks prior to testing or a recent thoracic or abdominal surgical procedure. Parents were instructed not to use lotion on their infant's face or an oil-based hair preparation prior to testing that would prevent a tight seal when putty was applied. Infants received chloral hydrate (60–100 mg/kg; maximum

dose, 1.0 g) orally or rectally.^{16,24} Hydroxyzine (0.25–0.5 mg/kg) was added for a synergistic sedative effect for toddlers weighing 11 kg or more.¹⁶ The Infant Pulmonary Function Laboratory sedation policy and precautions were adopted. Infants were continuously monitored during the study with a pulse oximeter. The ethics committee of the institution approved the testing protocol. Informed written parental consent was obtained for each infant prior to testing and parents were present during the tests.

Testing Protocol

The infant was weighed before the chloral hydrate was given and two trained adults performed the stature measurement after completing the ILFT.¹⁶ Once asleep, the infant was placed supine on the testing table,²⁵ and a shoulder roll tilted the head back gently into a “sniffing” (neutral) position.^{16,26} The nasal vestibules were inspected using a flash light and inspissated mucus was pulled out using a fine-tipped forceps, and an ear curette that had a flexible loop with a 4 mm tip (“White FlexLoop,” Bionix Development Corporation, Toledo, OH). The appropriate size transparent face mask was embedded in silicone putty and placed over the infant’s mouth and nose and an airtight seal was achieved.^{16,17} The investigator held the valve assembly connected to the facemask to maintain an adequate yet gentle pressure on the mask against the infant’s face to prevent airleaks. He simultaneously exerted a gentle coordinated anterior thrust on the lower jaw which facilitated gas flow through the upper airways of the sedated infant.^{26–29} In between measurements, the valve assembly was disconnected from the mask. The mouth and nares were inspected through the mask port to ensure that they were not obstructed by putty. Without having to remove the mask, putty was pushed away from an airway opening by inserting a 6-inch long wooden stick (Allegiance Cotton-Tipped Applicators; Cardinal Health McGaw Park, IL) into the mask port. A cannula carrying 2 L/min airflow was inserted into the mask port to expedite the restoration of the normal fractional alveolar N₂ concentration (0.79),^{16,17} and prevent the deadspace effect on the FRC_{dyn}.³⁰ In each infant, we attempted to obtain 2–3 FRC_{dyn}, and 2 FRC_{st} measurements. The FRC_{dyn} was measured before the FRC_{st} to prevent lung inflations from affecting the EEL. In some infants, 1–2 FRC_{dyn} measurements were also obtained after the FRC_{st} in order to determine if the previous lung inflations would affect the (dynamic) EEL. A period of at least twice the washout time was allowed between FRC measurements.^{16,17}

FRC Measurement by MBNW

The Pediatric Pulmonary Unit (PPU) 2600 (Sensor-Medics, Anaheim, CA) was used to measure FRC_{st} and FRC_{dyn} by the bias flow open-circuit N₂ washout technique.^{16,17,31,32} The methodological aspects of the validated technique used, were described elsewhere.^{16,17,32,33} A custom-made computer-controlled system (CCCS) was used to adapt the PPU for measuring the FRC_{dyn} as previously described.^{16,32} Basically, when a stable tidal breathing was observed in real-time on the computer monitor screen, the slide valve was activated, switching infant into the constant bias flow of pure O₂ as close to end-expiration as possible. When the washout was completed, the slide valve was activated, switching the infant back to breathing room air.^{16,17,32} In this investigation, we used a T-shaped valve unit made of a one-way mini-balloon valve attached to a calibrated and heated 0–160 L/min screen pneumotachometer Hans Rudolph, Inc., Kansas City, MO) (PNT) that was connected via a deadspace reducer connection to a three-way pneumatic slide valve assembly.

When measuring the FRC_{st}, a Y-adaptor carrying a 4–15 L/min bias airflow was connected to the mini-balloon valve. Manual hyperventilation was performed by intermittent thumb occlusions of the expiratory limb of the Y-adaptor which diverted the bias airflow through the balloon valve, PNT and facemask causing lung inflations.¹⁶ Lung inflation was initiated during a tidal inspiration, and the rate of inflation was adapted to the individual infant’s

breathing pattern. Several progressive rapid inflations were delivered to the infant's lungs until the infant's respiratory drive was inhibited.^{16,22,23} Inflations were generally limited to a Pao of 20–25 cm H₂O in order to minimize the risk of aerophagia. The infant often spontaneously generated one large sigh breath overriding one of the manual inflations,³⁴ which was then allowed to be completed uninterrupted by quickly terminating the thumb occlusion of the expiratory limb of the Y-adaptor. Inflations were then quickly resumed at end-expiration to smoothly induce the PHA. The display of flow (F), Pao and flow-volume loops signals in real time on the CCCS computer monitor screen enabled the operator to activate the slide valve after end-passive expiration within 1–8 sec into the PHA and switch the infant to breathing pure oxygen before he/she resumed inspiration. Recorded signals were analyzed on the CCCS computer to confirm that the lungs were indeed at EEV by observing a zero flow signal baseline when the infant was switched into oxygen.¹⁶ Figure 1 shows passive expiratory flow-time and airway opening pressure-time traces from two infants that were recorded during the FRC_{st} measurement. The traces demonstrate that the switch into pure O₂ occurred during the post-expiratory apnea, and since the infant was then no longer breathing through the PNT, it caused the following: (1) an abrupt upward shift in baseline of the Pao tracing from zero to 0.57 cm H₂O generated by the constant bias flow of O₂;¹⁶ and (2) the disappearance of tiny waves in the flow trace zero baseline which originated from rhythmic myocardial relaxations and contractions causing minute compressions and decompressions of contiguous lungs and airways that generated miniscule changes in airflow that were transmitted to the PNT. The frequency of these miniscule peaks was 1.63 or 98 (Fig. 1A), and 2.12 Hz or 127 beats per min (Fig. 1B), respectively, which was comparable to the simultaneously monitored heart rate by the pulse oximeter.

The switching error above the FRC_{dyn} was estimated, and when appropriate, converted to BTPS.^{16,17} The deadspace of the facemask and apparatus were subtracted as described elsewhere.^{16,17,33} The FRC_{st} and error-corrected FRC_{dyn} were converted to BTPS.^{16,17} The author and his assistant independently performed the data analysis.

The latent period, which is the number of seconds from the time the infant was switched into O₂ to initiate the washout until the point of rise above baseline of the N₂ washout curve displayed in real-time on the PPU computer monitor screen, was recorded. The “actual” washout times (*t*), *t*FRC_{st} and *t*FRC_{dyn}, were obtained by subtracting the latent period from their respective total washout time.¹⁶

Statistical Analysis

Means of FRC_{st}, FRC_{dyn}, *t*FRC_{st}, and *t*FRC_{dyn}, 95% confidence intervals (CI), and coefficient of variation (CV) were computed. Paired measurements were compared using the Student's *t*-test. *P* values of less than 0.05 for a two-tailed test were regarded as significant. Table 1 includes individual FRC_{dyn} and FRC_{st} measurements obtained from each infant. Mean FRC and washout time were presented as scatter plots against their respective infant's height. Linear regression lines were fitted to the FRC data. The bias and limits of agreement between FRC_{dyn} and FRC_{st} were calculated.³⁵

RESULTS

Five infants woke up after their first FRC_{st} measurement had been obtained. Given the exceptionally high repeatability of all measurements in the cohort (Table 1), they were included in the data analysis. Their inclusion did not skew the outcome (see below).

FRC_{st} and FRC_{dyn} measurements were highly repeatable (Table 1). There was also intrasubject overlap of individual measurements between the FRC_{st} and FRC_{dyn} (Table 1), and the difference was statistically insignificant (*P* = 0.2839; paired *t*-test); the geometric

means of the CV were 1.6 and 2.2%, respectively. Mean FRC_{st} (95% CI) was 21.1 (20.0 to 22.3) and error-corrected FRC_{dyn} was 21.4 (20.4 to 22.4) ml/kg. Means of FRC_{st} and FRC_{dyn} exhibited body height (Fig. 2), weight, and age (data not shown) dependence. Furthermore, the FRC_{dyn} measurements, which were obtained after the FRC_{st} in seven infants, were not affected by previous lung inflations (Table 1). The PHA was successfully induced, and repeatable FRC_{st} measurements were obtained in seven lightly sedated infants who were about to wake up and had an irregular tidal breathing (Table 1).

The N_2 washout curve of FRC_{st} rose above baseline after a mean latent period of 8 sec (95% CI 7–10) depending on the length of the PHA and the time the slide valve switched the infant into the pure O_2 during the apnea. The latent period for the FRC_{dyn} was 1–3 sec. The actual washout times were repeatable. Two intrasubject $tFRC_{st}$ were within 10% of each other in 22 of the 28 infants that had 2–3 FRC_{st} measurements. Two $tFRC_{dyn}$ were within 10% of each other in 28 of the 33 infants. Mean $tFRC_{st}$ and $tFRC_{dyn}$ were 60 sec (95% CI 55–65), and 47 sec (95% CI 43–51), respectively, and the difference was statistically significant ($P < 0.0001$; paired t -test). Means were positively correlated with the infant's respective height (Fig. 4), weight, and age (data not shown).

DISCUSSION

In the present study, we hypothesized that FRC_{st} would be a robust volume landmark because it would only be determined by the EEV of the sedated infant's respiratory system during the PHA. The high precision of the FRC_{st} measurements, which had a geometric mean CV of 1.6%, supported this hypothesis (Table 1). However, contrary to our second hypothesis, the finding of virtually no difference between the FRC_{st} and FRC_{dyn} (mean of differences, -0.31 ml/kg (95% CI -0.66 to 0.04)) was surprising (Table 1 and Figs. 2 and 3).

Technical Aspects

FRC_{st} Versus FRC_{dyn} —For many years, healthy infants have been assumed to have an increased tendency to airway closure and gas trapping during quiet tidal breathing. This physiologic assumption has been supported by reports of higher FRC values by body plethysmography (FRC_{pleth}) than by gas dilution techniques in healthy infants, but not in adults.^{2,14,18,36–40} Nevertheless, some authors thought the difference might also be due to a technical element in plethysmography.^{37,40} The transition from a dynamically maintained to a passively determined end-expiratory lung volume was estimated to occur at 1 year of age using respiratory inductive plethysmography. However, these measurements, which were made in the subjects' homes, had considerable intra- and inter-subject variability.⁹

When measuring the FRC_{st} , the switch into O_2 was delayed as much as possible during the post expiratory apneic pause to ensure the following: (1) complete passive exhalation; (2) stabilization of the EEV since near end-exhalation would presumably have a very low expiratory airflow with likely imperceptible changes in the flow signal baseline in real-time on the computer monitor screen; and (3) elimination of any hyperventilation-induced positive end-expiratory pressure (PEEP) that might increase measured FRC_{st} .^{25,41–43} The precision of FRC_{st} measurements was not affected by the number of lung inflations. If an infant had on occasion resumed breathing during the PHA at the time of switching into the O_2 bias flow, the FRC_{st} was easily corrected for that switching error above the FRC_{st} level (EEV) without affecting its precision (personal observations). In the PPU washout circuit, switching the infant into pure O_2 was associated with a trivial rise in Pao to 0.57 cm H_2O (Fig. 4).¹⁶ PEEP is known to raise the lung volume, and one would anticipate it could artificially increase measured FRC_{st} .^{25,41–43} However, this was not the case in our study because the 0.57 cm H_2O was induced by pure O_2 , not air. Therefore, the actual amount of

N₂ gas in the lungs and airways during the post-expiratory apnea, which the N₂ emission spectrophotometer would measure after switching the infant into the bias flow of O₂, remained unaltered. A previously reported mean FRC_{dyn} by MBNW was comparable to ours.³⁹

FRC Washout Time—When measuring the FRC_{dyn}, a latent period of 1–3 sec during the MBNW varied with all of the following: the bias O₂ flow rate; the dead space volume of the facemask and apparatus; the length of the distal washout tubing from the infant to the N₂ mixing chamber and the N₂ emission spectrophotometer; the size of the mixing chamber; and the infant's tidal breathing.^{16,17,32} In the present study, the intrasubject latent period was longer for the FRC_{st} than FRC_{dyn} in all measurements due to the PHA. After the infant was switched into the pure O₂ during the post-expiratory apneic pause to measure the FRC_{st}, the spontaneous breathing invariably resumed with very small tidal breaths that slowly increased in volume and rate as gauged by the breathing bag's intermittent deflations.^{16,32} This initial hypopnea accounted for the slow rise in the FRC_{st} washout curve and the longer *t*FRC_{st} than *t*FRC_{dyn} (Figs. 1 and 4).¹⁶ In vitro simulation with the calibrating syringe confirmed these two in vivo observations without affecting the measured known volume.³²

Rather than adjusting the bias O₂ flow rate to twice the infant's tidal inspiratory flow rate, we have always used a precisely adjusted doubly checked fixed O₂ rate of 10 L/min for all infants weighing more than 5.0 kg, as well as identical washout circuits. Therefore, the reliability of future measurements on the same infant would be enhanced when tracking the lung growth and development in prospective studies.^{16,17,32,33,44–46} In our study, repeatable *t*FRC_{st} and *t*FRC_{dyn}, which exhibited height (Fig. 4), weight, and age dependence, might become useful indicators of airway obstruction and ventilation inhomogeneity.^{47,48} Sedation could potentially cause hypopnea and prolong the washout times, but tailoring the drug dose to the individual infant and monitoring the tidal breathing minimized this effect (Fig. 4).³²

Factors Affecting N₂ Washout—Breathing pure O₂ did not progressively lower measured FRC even when 5–8 washouts were performed in individual infants (Table 1).^{16,49} Inadvertent excessive pressure on the facemask could cause upper airway obstruction resulting in premature return of the N₂ washout curve to baseline. Consequently, the measured FRC would be underestimated if the washout were then terminated.³² Hypopnea during peak sedation could also result in an ineffective or incomplete washout. Hence, the constant monitoring of the breathing bag's intermittent deflations was essential.^{16,32} Monitoring chest wall excursions, and when the infant was breathing through the PNT, the tidal breathing displayed in real-time on the monitor screen was also critical since hypopnea emerging during the waiting period necessitated its extension to 3–4 times the washout time before initiating the next measurement. Sedation could conceivably depress the mechanisms maintaining an elevated FRC_{dyn} and enhance airway closure in the supine infant at lower lung volumes during testing.⁴⁴ However, our findings suggest that the FRC_{dyn} was not affected as long as the tidal breathing was monitored. During the MBNW, inadvertent occlusion by putty of one nasal opening of the young infant who is a preferential nose breather, or of the mouth of a snoring toddler resulted in an inaccurately small FRC (personal observations).^{14,16–18,32,50}

Premature switching of the infant into O₂ before end-passive expiration generated a tiny transient peak at the onset of the N₂ washout caused by exhaled residual gas, followed by the latent period. The actual washout began when the infant resumed his/her tidal breathing; however, the measured FRC_{st} was overestimated (personal observations).

Physiological Aspects

Thorsteinsson et al.⁴¹ reported a mean FRC of 17 ml/kg measured by the sulfur hexafluoride (FRC_{SF6}) washout technique under halothane anesthesia and paralysis in 21 healthy infants. The ventilator setting was switched to zero PEEP 0.5–2 min before the SF₆ washout.⁴¹ In the present study, PEEP was zero at the time of switching the infant into the bias flow of pure O₂ during the PHA to measure the FRC_{st} (Fig. 1). Our mean FRC_{N2} is comparable to a mean FRC_{SF6} of 21.3 ml/kg reported by von Ungern-Sternberg et al.,⁴³ which was measured with an ultrasonic flowmeter in healthy intubated infants under propofol anesthesia without using PEEP or neuromuscular blockade. Following neuromuscular blockade, mean FRC_{SF6} decreased to 12.2 ml/kg and the lung clearance index increased.⁴³ Regli et al.²⁵ reported a mean FRC_{SF6} of 22.2 ml/kg in the supine position which decreased to 19.5 ml/kg after adopting the Trendelenburg position in 20 children under anesthesia with neuromuscular blockade. The lung clearance index increased too.²⁵ However, in both studies, a continuous bypass flow was needed to ensure an exact uninterrupted delivery of the SF₆.^{25,43} The bypass flow generated a constant PEEP of 3 cm H₂O in the breathing circuit which might have impacted the FRC_{SF6} measurements.^{25,43} Thus, compared to FRC measurements performed under chloral hydrate sedation in the present study, studies under anesthesia differ and could be affected by multiple factors such as: (1) uneven pulmonary atelectases resulting from anesthesia induction, mechanical ventilation, and the use of muscle relaxant drugs;^{25,26,41–43} (2) constant application of PEEP;^{25,41–43} (3) anesthesia-induced inactivation of HBIR and low respiratory drive;⁵¹ (4) using an endotracheal tube instead of a facemask, which removes the laryngeal defense mechanism to brake expiration,¹⁸ bypasses the supraglottic airways, and entails accounting for a different dead space correction volume;^{16,17,33} and (5) supine versus Trendelenburg positioning.²⁵ The highly compliant chest wall relies on muscle tone in infants; hence, muscle paralysis during anesthesia would be expected to result in a much smaller FRC than in older children.^{1,18,25,41–43} The chloral hydrate sedation, in doses normally used for lung function testing, did not affect the strength of the HBIR in healthy infants.⁵² Hershenson et al.²⁷ reported that hypnotic doses of chloral hydrate preferentially depressed genioglossus activity, suggesting the drug exhibited muscle relaxant properties. In the present study, FRC_{st} measurements that were obtained towards the end of testing in seven lightly sedated infants were not different from earlier measurements when the level of sedation was deeper, suggesting no significant drug-induced respiratory muscle relaxation (Table 1).

Vocal cords adduction was reported during voluntary breath-holding in awake healthy adults.⁵³ Sustained active glottal closure was also reported in central apneas in newborn infants and mammals.⁵⁴ In the present study, the persistence of glottic closure under the muscle relaxant effect of chloral hydrate sedation during the PHA seemed unlikely because of the ease with which lung inflations were repeatedly initiated, and smoothly progressed in each infant.^{27,28,44} Actually, we think that lung inflations in our healthy infants might have had an effect similar to nasal continuous positive airway pressure (NCPAP) on the EEL by abolishing breathing strategies to prevent airway closure.⁵⁵ Moreover, if the glottis were to be closed, gastric insufflation would have probably occurred more frequently during lung inflations due to the diversion of the inflating airflow to the esophagus, but it did not. In our healthy infants group, we think the PHA had, indeed, effectively abolished the sedated infant's breathing strategies such that at end-expiration, his/her respiratory system was at EEV whether the switching into O₂ was performed within 1–2 sec or delayed for several seconds after the onset of the end-expiratory apnea (Fig. 1). Furthermore, the infant lungs empty four times faster than adults.⁵⁶ Nevertheless, laryngeal electromyography or ultrasonography would provide an ultimate confirmation of our presumption.^{54,57–60} Our findings are in agreement with a recent study that reported FRC_{pleth} measurements which accounted for the deadspace of the facemask among other volume errors.^{33,40} The authors

concluded that previous equations had overestimated FRC_{pleth} , and that new reference data ought to be generated for healthy infants, and they cast doubt on air trapping in healthy infants.⁴⁰ Thus, the overlap between FRC_{dyn} and FRC_{st} along with the high repeatability of the measurements (Table 1) indicated that air trapping unlikely existed in our healthy infants.^{2,11,36–40}

Study Limitation and Safety Aspects—Our study was limited by the lack of young full-term neonates or premature infants whose inherent rapid breathing, maximally active HBIR, and increased active or rapid eye movement (REM) sleep time, could render the induction of a PHA difficult or potentially undesirable.^{3,7,10,13} Previous studies often performed on unsedated infants reported a substantial dynamic elevation of the FRC in this population.^{3–6,10–13,36,38,44}

All infants in the present study remained clinically stable during and after testing. Following the brief PHA, the infant always spontaneously resumed his/her tidal breathing which suggested that the circulating carbon dioxide level of a mild hypocapnea was being restored.^{23,61} Contrary to the prolonged hyperventilation often reported in the literature,^{19,20,62} brief periods of hyperventilation were not associated with changes in cerebrospinal bicarbonate.⁶³ If desired, gentle rubbing of the infant's ear pinna promptly terminated a PHA with the resumption of spontaneous tidal breathing, even during peak sedation (personal observation). The level of sedation employed was not different from the level used in usual infant lung function testing. As a sedative-hypnotic drug, chloral hydrate can depress the central respiratory drive.⁶⁴ Deeper sedation was avoided because it could cause a prolonged hypopnea resulting in ineffective N_2 washout. The N_2 washout curve could then fail to rise above baseline in real time on the computer monitor screen, and the washout may need to be aborted.^{16,32} Infants aged 1–2 months seemed unpredictable in terms of the depth of sedation that could be achieved when using comparable weight-appropriate chloral hydrate doses (personal observations).

Advantages of Measuring the FRC_{st} —(1) The FRC_{st} was a reliable volume landmark that seemed determined only by the EEV of the infant's respiratory system; (2) it eliminated potential sources of error associated with measuring the FRC_{dyn} ,^{16,17} including the PNT dead space effect on the FRC_{dyn} level;^{17,30} and (3) contrary to the FRC_{dyn} , the FRC_{st} was not influenced by the sleep state (Table 1). An investigator challenged by time constraints imposed by the limited period of drug-induced sleep has to wait until the infant has settled into regular tidal breathing during quiet sleep before attempting a FRC_{dyn} measurement.^{16–18,44,46} Larger studies on healthy infants and those with lung disease are needed to generate normative data and regression equations, and to explore the clinical usefulness of measuring the FRC_{st} .

In conclusion, we developed a simple, novel, non-invasive and reliable technique for measuring the FRC_{st} by the MBNW by inducing a brief PHA in spontaneously breathing sedated infants. In our cohort of healthy infants, highly repeatable FRC_{st} , FRC_{dyn} , $tFRC_{st}$, and $tFRC_{dyn}$ measurements exhibited height, age and weight dependence. Contrary to our second hypothesis, intrasubject FRC_{st} and FRC_{dyn} measurements often overlapped even in the younger infants, so augmentation of FRC_{dyn} seems improbable or minor. Consequently, the present study casts significant doubt on the established physiology of the trapped gas hypothesis in healthy infants. The FRC_{st} could easily be incorporated into routine studies investigating the FRC_{N_2} in various respiratory diseases and disorders, in infants or in animals, since it eliminates potential sources of errors and disadvantages associated with measuring the FRC_{dyn} . This, in turn, would facilitate interlaboratory comparisons of data, especially in multicenter studies.

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Fig. 1.

Measuring the static (FRC_{st}) functional residual capacity. Two traces from infants no. 30 (A) and 33 (B) focus on the time period that begins with end passive expiration of the last lung inflation at 1.18 and 1.98 sec, and ends at 16.2 and 14.2 sec, respectively. Each includes a trace of flow and airway opening pressure (Pao); inspiration is positive and expiration is negative. End-passive expiration begins when Flow and Pao are zero signaling the onset of apnea which lasts about 14 and 8.25 sec, respectively. The slide valve switches the infant into the bias flow of O_2 at 7.78 and 8.39 sec, respectively, causing an abrupt upward shift in baseline of the Pao tracing from zero to 0.57 cm H_2O . The infant no longer breathes through the PNT. The onset of the first negative deflection (inspiration) in Pao at 15.7 and 10.5 sec that is 7.92 and 2.11 sec after switching the infant into O_2 , respectively, indicates the start of N_2 washout.¹⁶

Fig. 2. Means of static (FRC_{st} [$\times$]) (passive) and dynamic (FRC_{dyn} [$\circ$]) functional residual capacity (FRC) along with regression lines are plotted against the respective infant's height and exhibiting dependence (* slope, Y-intercept). Note a trivial difference between the regression lines in younger infants, and the lines merge in older toddlers.

Fig. 3.

A Bland–Altman plot shows the distribution of the differences between the static (FRC_{st}) (passive) and dynamic (FRC_{dyn}) functional residual capacity as percent of their average. The horizontal solid line represents the mean % difference and the broken lines the 95% limits of agreement of the observed % differences. The dotted line is for zero (line of identity).

Fig. 4. Washout times (t). Means of $tFRC_{st}$ ($\times$) and $tFRC_{dyn}$ ($\circ$) are plotted against the respective infant's height and exhibiting dependence. Note the longer intrasubject $tFRC_{st}$ than $tFRC_{dyn}$.

TABLE 1

Individual FRC Measurements

Infant No. ^a	FRC _{dyn} ^b			FRC _{st} ^b
1	325.1	337.2	328.2	321.7
2	316.5	315.6		316.4 ^d
3	304.2	278.2		320.0
4	277.8	264.4	257.5	306.1
5	220.4	218.4	229.1	260.5
6	212.5	212.7	229.7	258.5
7	215.0	211.2	231.0	229.0
8	207.6	214.0	213.8	235.5
9	256.9	241.1	235.7	186.1
10	218.3	238.0		199.2
11	197.8	215.5	196.1	203.4
12	170.3	165.8		203.9
13	158.1	165.9		213.1
14	203.9	211.8		222.8
15	184.5	194.3	191.5	219.4
16	150.1	146.5	147.1	236.8 ^e
17	166.0	162.9	151.0	229.8
18	163.7	163.3	168.9	221.4
19	164.2	159.0		215.3
20	141.4	149.5	147.5	174.9
21	143.9	140.1		168.0
22	108.6	103.2	99.6	163.8
23	139.9	150.8	140.6	204.7
24	139.3	136.6	133.6	195.5
25	118.9	122.1	120.9	187.3
26	124.5	133.1	128.9	157.8
27	101.6	104.0		153.6
28	130.2	132.1	127.0	147.8
				154.1
				152.0
				142.1
				137.7
				141.7
				144.1
				143.5
				92.80
				104.4
				97.9
				155.0
				144.4
				140.2
				137.3
				134.1
				121.7
				124.9
				118.3
				102.9
				103.4
				127.9
				127.7

Infant No. ^a	FRC _{dyn} ^b				FRC _{st} ^b
29	97.8	94.8	92.4	102.2	93.9
30	115.6	121.4	120.7	108.2	113.1
31	117.7	118.8	114.0	109.5	
32	108.6	107.5		109.8	
33	111.8	119.3	117.0	112.7	108.1

^a Infants no. 19 and 21–33 are 21 weeks old or less.

^b Note that the first and second intrasubject FRC_{dyn} as well as the first and second FRC_{st} are within 5% of each other in most subjects, and within 10% in the others.

^c Italic numbers: FRC_{dyn} was measured after the FRC_{st} measurements.

^d Bold numbers: FRC_{st} was measured towards the end of testing when the infant became lightly sedated and had an irregular tidal breathing.

^e Five infants woke up after their first FRC_{st} measurement had been obtained. Each of these single FRC_{st} values is within 10% of the respective intrasubject mean FRC_{dyn}.