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Comprehensive integrated spirometry using raised volume passive and forced expirations and multiple-breath nitrogen washout in infants

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Abstract

With the rapid somatic growth and development in infants, simultaneous accurate measurements of lung volume and airway function are essential. Raised volume rapid thoracoabdominal compression (RTC) is widely used to generate forced expiration from an airway opening pressure of 30 cm H₂O (V_{30}). The (dynamic) functional residual capacity (FRC_{dyn}) remains the lung volume most routinely measured. The aim of this study was to develop comprehensive integrated spirometry that included all subdivisions of lung volume at V_{30} or total lung capacity (TLC_{30}). Measurements were performed on seventeen healthy infants aged 8.6–119.7 weeks. A commercial system for multiple-breath nitrogen washout (MBNW) to measure lung volumes and a custom made system to perform RTC were used in unison. A refined automated raised volume RTC and the following two novel single maneuvers with dual volume measurements were performed from V_{30} during a brief post-hyperventilation apneic pause: (1) the passive expiratory flow was integrated to produce the inspiratory capacity (IC) and the static (passive) FRC (FRC_{st}) was estimated by initiating MBNW after end-passive expiration; (2) RTC was initiated late during passive expiration, flow was integrated to produce the slow vital capacity ($jSVC$) and the residual volume (RV) was measured by initiating MBNW after end-expiration while the jacket (j) was inflated. Intrasubject FRC_{dyn} and FRC_{st} measurements overlapped ($p = 0.6420$) but neither did with the RV ($p < 0.0001$). Means (95% confidence interval) of FRC_{dyn} , IC, FRC_{st} , $jSVC$, RV, forced vital capacity and tidal volume were 21.2 (19.7–22.7), 36.7 (33.0–40.4), 21.2 (19.6–22.8), 40.7 (37.2–44.2), 18.1 (16.6–19.7), 40.7 (37.1–44.2) and 10.2 (9.6–10.7) ml/kg, respectively. Static lung volumes and capacities at V_{30} and variables from the best forced expiratory flow-volume curve were dependent on age, body length and weight. In conclusion, we developed a comprehensive physiologically-integrated approach for in-depth investigation of lung function at V_{30} in infants.

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Keywords

forced expiration; lung volume; residual volume; functional residual capacity; slow/forced vital capacity; total lung capacity; inspiratory capacity; inspiratory/expiratory reserve volume; infant or animal lung function; inert gas/nitrogen washout; genetic/environmental assessment

1. Introduction

With the rapid somatic growth and development in infants and changes in clinical status in those with disease, an impeccably high degree of repeatability and accuracy of simultaneous measurements of lung volume and airway function is essential in detecting and quantifying the earliest pathophysiological changes. Forced expiration has been generated in infants from end-tidal inspiration with the rapid thoracoabdominal compression (RTC) technique. However, forced expiration is now widely performed by RTC from a raised lung volume to an airway opening pressure (P_{ao}) of 20 but mostly 30 cm H₂O (V_{30}). Raised volume RTC generates the forced vital capacity (FVC) and forced expiratory flow-volume (FEFV) curves in which flow limitation is most often achieved. The jacket placement and the need to repeat the raised volume RTC using increasing jacket pressures (P_j) until flow limitation is achieved may alter lung mechanics or influence other measurements (Mead, 1980; Turner et al., 1995; Feher et al., 1996; Morris, 1999b; Castile et al., 2000, 2004; Jones et al., 2000; Sly et al., 2000; Beardsmore et al., 2001; Goldstein et al., 2001; Lum et al., 2001, 2002a, 2002b, 2004b, 2006; Hoo et al., 2002, 2004; Ranganathan et al., 2002a, 2002b; ATS/ERS Statement, 2005; Stocks, 2006; Linnane et al., 2008; Loland and Bisgaard, 2008). Attempts were made to assess total lung capacity (TLC) from measurements of crying vital capacity and residual volume (RV) but the (dynamic) (FRC_{dyn}) functional residual capacity (FRC) has been the lung volume most routinely and reliably measured. FRC has been measured by plethysmography (FRC_{Pleth}) and the multiple breath nitrogen washout (MBNW) technique and other inert marker gases such as sulfur hexafluoride and helium (Gaultier et al., 1979; Gappa et al., 1993; Quanjer and Stocks, 1995; Wauer et al., 1998; Morris, 1999b, 2009; Stocks, 1999, 2006; Morris et al., 2001; Castile et al., 2000, 2004; Hülskamp et al., 2006, 2009; Stocks et al., 2001, 2007; Robinson et al., 2009). Tidal breathing parameters neither reliably discriminated between healthy infants and the ones with lung disease nor distinguished types or levels of respiratory dysfunction. (Clarke et al., 1994; Seddon et al., 1996; Paetow et al., 1999; Schmalisch et al., 1999, 2005; Ranganathan et al., 2003). We previously reported measurements of fractional lung volumes and total lung capacity (TLC) at V_{30} in infants with cystic fibrosis (Morris, 1999b). Precise measurements of the FRC_{dyn} and the RV were obtained by the MBNW; the difference between mean values was the expiratory reserve volume (ERV). Total lung capacity ($fTLC$) was the sum of the forced (f) vital capacity (FVC) generated from V_{30} and the RV (Morris, 1999b). In addition to the FRC_{dyn} , we reported measurements of the (passive) static FRC (FRC_{st}) by MBNW by inducing a brief post-hyperventilation apnea (PHA) in sedated, spontaneously breathing healthy infants. The FRC_{st} was not different from the FRC_{dyn} (Morris, 2009). Castile et al. (2000) reported fractional lung volumes and TLC that were estimated from three measurements: (1) FVC by raised volume RTC from V_{30} ; (2) FRC_{Pleth} ; and (3) the expiratory reserve volume (ERV). However, several studies have questioned the accuracy of FRC_{Pleth} measurements in infants (Hammer et al., 1998; Hülskamp et al., 2003; Broughton et al., 2006, 2007; Poorisrisak et al., 2009). Techniques that entail inflating the lungs to an inspiratory pressure of +40 cm H₂O (V_{40}), such as the forced deflation technique, have a major limitation; they can only be used in intubated subjects who are heavily sedated and paralyzed (Motoyama, 1977; Hammer and Newth, 1996, 1997, 2005; Hammer et al., 1998; von Ungern-Sternberg et al., 2009).

Therefore, we thought that comprehensive integrated lung function (CILF), which incorporated precise measurements of the FVC and static lung volumes and capacities (Sly et al., 2008) at V_{30} , would be an ideal approach for routine investigation in sedated, spontaneously breathing infants. CILF would be accomplished by combining in single maneuvers the volumes integrated from the pneumotachometer flow measurements with those measured indirectly by MBNW (Morris, 1999a, 1999b, 1999c, 2009; Morris et al., 2001; Robinson et al., 2009). Our main hypothesis was that CILF would enable the analysis and investigation of the relation between measurements, such as a dynamic and a static volume or two static volumes, not only intrasubject but also within a single maneuver. The primary aims of this study were to present the methodological aspects of our novel physiologically-integrated approach, which included a refined raised volume RTC technique, and apply it to a group of healthy infants. The basic underlying concept of this investigation was the induction of a brief PHA (Eldridge, 1973; Mangin, 1982; Feher et al., 1996; Morris, 1999b, 2009; ATS/ERS Statement, 2005). Having the squeeze jacket unfastened, we hypothesized that during a PHA the passively exhaled gas volume from V_{30} measured by a pneumotachometer (PNT) would be the inspiratory capacity (IC). The IC is the volume at V_{30} above the elastic equilibrium volume level of the infant's respiratory system. The remaining gas volume is the FRC_{st} measured by MBNW (Morris, 2009). Total lung capacity (TLC) would be the sum of the IC and FRC_{st} measurements from a single maneuver. By measuring the intrasubject RV by MBNW (Morris, 1999b) and the TLC, we hypothesized that the difference between the two measurements would be a reliable estimate of the slow vital capacity (SVC) made for the first time in infants. We also obtained another estimate of the slow vital capacity ($jSVC$) by activating jacket (j) inflation late during the passive expiration from V_{30} when the RV was measured (Morris, 1999b). The $jTLC$ would be the sum of $jSVC$ and RV from a single maneuver. We hypothesized that as long as the jacket did not limit chest wall expansion, the $jSVC$ should be equal to SVC. We also hypothesized that the total lung capacity measured in three different ways, namely, the TLC, $fTLC$ and $jTLC$ would be comparable in this healthy infant cohort. Finally, we hypothesized that measured volumes and capacities at V_{30} would be related to the respective infant's anthropometric measurements.

2. Methods

2.1. Subjects

Measurements were performed on 14 Caucasian (8 boys) and 3 black (1 boy) healthy infants and young children (Table 1) participating in a respiratory physiology study (Morris, 2009). Median (range) age was 38.6 (8.6 – 119.7) weeks, weight was 8.99 (5.77 – 12.35) kg and body length was 72.5 (58.9 – 95.3) cm. 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.

2.2. Testing protocol

Preparing the infant for testing, weight and stature measurements, positioning and monitoring during testing were detailed elsewhere (Morris, 1999b, 2009). Infants received chloral hydrate (60–100 mg/kg; maximum dose, 1.0 gm) orally or rectally (Treluyer et al., 2004). For toddlers weighing 11 kg or more, hydroxyzine (0.25–0.5 mg/kg) was added for a synergistic sedative effect (Morris 1999b, 2009). The lower jaw was depressed to keep the mouth slightly open. The appropriate size transparent facemask was embedded in a thick roll of firm putty that was applied around the mouth and nose. The roll of putty crossed over the nasion carefully avoiding the cartilaginous segment of the nasal septum. This segment could collapse and obstruct the anterior nasal passages especially in black infants because of their short nasal bridge (Ofodile, 1993). During testing, the investigator placed one hand around

the infant's mandible and supported it. His fingertips often exerted a gentle pressure on the infant's cheeks between the upper and lower jaw to ensure that the mouth remained constantly slightly open. This approach was particularly crucial during lung inflations and forced expiration (personal observations). The investigator's other hand held the valve assembly connected to the clear facemask, applying a gentle pressure on the mask against the infant's face to maintain an airtight seal. Both hands exerted a gentle and coordinated anterior thrust on the lower jaw while keeping the neck slightly extended (Green et al., 1974; Mead, 1980; Motoyama, 1992; Isono, 2006; Morris, 2009). A cannula carrying 2 L/min airflow was inserted into the mask port after the valve was disconnected in-between tests (Morris, 1999b, 2009; Morris et al., 2001).

2.2.1. Sequence of tests—Generally, the FRC_{dyn} was measured first (Morris, 1999b, 2009; Morris et al., 2001) then the $jSVC$ -RV followed by either the IC- FRC_{st} or raised volume RTC. Nevertheless, the sequence of various tests was often adapted to the individual infant. The raised volume RTC was performed when the infant was deeply sedated. The FRC_{dyn} was measured when he/she was lightly sedated but had settled into quiet breathing. The chloral hydrate sedation occasionally caused hypopnea with inefficient N_2 washout (Morris, 1999a, 1999b, 2009), so in these cases the raised volume RTC was performed instead. At peak sedation, an infant might have an increased tendency either for airway collapse that caused flow transients during forced expiration or for gastric insufflation during lung inflations, so the FRC_{dyn} was then measured instead. Deeper sleep occurred sometimes later during testing and was ascribed to delayed drug absorption by residual milk or formula in the stomach (personal observations). The sequence of tests has not affected measured FRC_{st} or FRC_{dyn} in healthy infants (Morris, 2009). Twenty-second epochs of tidal breathing were recorded throughout the testing.

2.3. Equipment

A commercial system, the Pediatric Pulmonary Unit 2600 (SensorMedics, Anaheim, CA, USA) was used to measure FRC and RV with the open-circuit bias flow N_2 washout technique. A custom made computer controlled system was used to measure the new IC and $jSVC$ and to adapt the commercial system for measuring the FRC and RV (Morris, 1999a, 1999b, 1999c, 2009; Morris et al., 2001). The custom made system was slightly modified to perform a refined automated raised volume RTC (see below).

In order to combine an accurate volume measurement integrated from the PNT flow signal with the indirectly measured volume by MBNW within a single maneuver, we designed a custom made 'T-valve' unit (Hans Rudolph Inc, Kansas City, MO). The T-valve was made of three components (Fig. 1) which allowed the commercial and the custom made systems to be used in unison: (1) a pneumatic three-way slide valve assembly that was leak-free and did not allow gas mixing between ports while the piston was sliding; (2) a 0–160 L/min heated screen pneumotachometer (PNT); and (3) a one-way mini-balloon valve. The infant breathed air through the PNT in the straight-through path of the T-valve that had a constant 13.97 mm flow-bore which was equal to the internal diameter of the PNT (Fig. 1A). Therefore, the PNT yielded accurate flow hence volume measurements. During the MBNW, the infant breathed pure O_2 from a 10 L/min constant bias flow through the T-valve's perpendicular path (Fig. 1B) that had a small dead space volume of 8.27 ml. Although raised volume RTC could be performed with the T-valve unit, we preferred to disconnect the slide valve and use only the assembled mini-balloon valve and PNT (Fig. 1C).

2.4. Single maneuvers with dual volume measurements at V_{30}

The constant bias airflow (5–15 L/min) circulating through the Y adapter was adjusted according to the infant's age and size. The airflow rate varied slightly during testing

according to the tidal breathing pattern, depth of sedation and tolerance. Using intermittent thumb occlusions of the expiratory limb of the Y adapter (Fig. 1A), the investigator delivered several rapid inflations to the infant's lungs until a PHA was induced (Feher et al., 1996; Morris, 1999b, 2009; ATS/ERS Statement, 2005). The last manual lung inflation was maintained until a Pao plateau was primarily observed at V_{30} and the inspiratory flow ceased to rise in real time on the custom made system's computer monitor screen. The occlusion of the Y adapter's expiratory limb was then terminated:

2.4.1. Measuring the inspiratory capacity (IC) (Figs. 1, 2A and 4) and the static (FRC_{st}) functional residual capacity—If the squeeze jacket had been applied to perform forced expiratory maneuvers, it was unfastened. By closely watching the flow signal and the flow-volume loop on the computer monitor screen, the investigator allowed passive expiration from V_{30} to be completed to the elastic equilibrium volume level of the infant's respiratory system. Passive expiration was entirely driven by the inward elastic recoil of the chest wall, the lung parenchyma and the surface tension of the alveoli. Flow was integrated to produce the IC and the expiratory time was recorded. Before the infant resumed spontaneous inspiration, the slide valve was activated after end-passive expiration switching him/her to breathing 100% oxygen (Fig. 1B) to measure the FRC_{st} by MBNW (Morris, 2009). The sum of the two variables from this single IC- FRC_{st} maneuver was the TLC. In each infant, we attempted at least two IC and FRC_{st} measurements (Fig. 5).

The intrasubject inspiratory reserve volume (IRV) was estimated as the difference between mean values of the tidal volume and the IC.

2.4.2. Measuring the slow vital capacity ($jSVC$) (Figs. 1, 2B and 4) and the residual volume (RV)—The squeeze jacket was fastened around the infant's chest and abdomen. Expiration from V_{30} was allowed to proceed passively at first. Jacket inflation was activated before the displayed flow signal reached zero baseline (end-exhalation) to induce a (partial) forced expiration down to residual volume. Flow was integrated to produce the slow vital capacity ($jSVC$) and the expiratory time was recorded. The RV was estimated by measuring the volume of N_2 expired after end forced expiratory switching of the inspired gas from room air to 100% oxygen while jacket inflation was maintained at the time of switching into oxygen during the post-expiratory apneic pause (Figs. 1B and 2B) (Morris, 1999b). The sum of the two variables from this single $jSVC$ -RV maneuver was the $jTLC$. In each subject, we attempted at least two $jSVC$ (Fig. 5) and RV measurements. Intrasubject ERV was calculated as the difference between mean values of the FRC_{dyn} and RV (Morris, 1999b, 2009).

2.5. Forced expiration from V_{30} by a refined automated raised volume RTC (Figs. 1, 3 and 4)

Instead of a fan pump (Morris, 1999b), automated lung inflation was performed with a new alternative pneumatic circuit made of a constant bias airflow (range 5–12 L/min) from a medical grade wall air source via a high precision flowmeter (Fig. 1C). Using the flowmeter's flow-control knob, the airflow rate was adjusted according to the infant's age and size. A safety pressure relief valve incorporated in the pneumatic circuit was then adjusted to release pressure at 32 cm H_2O (Fig. 1C).

Once manual hyperventilation had induced the PHA, one computer keystroke triggered automated raised volume RTC as follows: The (expiratory) balloon within the balloon valve inflated. The pneumatic circuit (Fig. 1C) inflated the lungs to the predetermined Pao (pPao) of 30 cm H_2O . Lung inflation was then automatically halted. The balloon airway occlusion (Fig. 1C) was maintained for 0.20 sec before activating jacket inflation. The automatic

jacket inflation was triggered at the end of the 0.20 sec airway occlusion. However, the balloon deflated after a fixed preset time delay of 0.05 sec (Fig. 3). Forced expiration then proceeded from V_{30} to RV (Morris, 1999b). In the present investigation, the jacket driving pressure or pressure transmission (P_{trans}) (Hayden et al., 1997; Morris, 1999b; ATS/ERS Statement, 2005) was kept at a minimum of about 0–3 cm H₂O (Fig. 3). If a higher pressure was generated in the first maneuver, P_{trans} was lowered by slightly loosening the jacket's firm vinyl outer layer. The software computed a 'true' actual Pao (aPao) by ensemble averaging of the Pao signal over the 0.20 sec occlusion period. After the first raised volume RTC, the aPao was measured. Further combined fine readjustments of the pneumatic circuit's airflow rate (Fig. 1C) and the pPao value (range, 30.1–30.6 cm H₂O) entered on computer were then necessary in order to obtain an aPao as close as possible or equal to 30.0 cm H₂O in subsequent maneuvers (Fig. 3). The automated last lung inflation was triggered in early passive expiration of the last manual inflation (breath stacking) which further facilitated the attainment of an aPao of almost 30.0 cm H₂O (Fig. 3). The raised volume RTC was repeated until flow limitation was achieved with no further increase in FEFV_{25–75} and FVC despite increasing applied jacket pressure. The best FEFV curve had the highest sum of FEFV_{25–75} and FVC (ATS/ERS Statement, 2005). In each subject, at least two FVC measurements within 10% of each other were obtained (Fig. 4). The aPao, the average Pj plateau and expiratory time were obtained from recorded signals. The rate constant for forced expiration was computed as the ratio of the differences in flows and volumes between 50 and 75% of the FVC ($RC_{50–75}$) (Tepper et al., 1999; Jones et al., 2000).

2.6. Minimizing aerophagia

Aerophagia has been an inherent risk of raised volume maneuvers especially during peak sedation. Without having to apply the Sellick maneuver (ATS/ERS, 2005), aerophagia was minimized by the following precautions (personal observations): (1) adjusting the infant's head and neck using a shoulder roll instead of a head ring (Morris, 1999b, 2009); (2) performing the anterior mandibular thrust and keeping an open mouth during raised volume RTC which minimized the diversion of the inflating airflow and the forced expiratory flow to the esophagus; (3) using an optimum bias airflow relative to the infant's age and size; (4) using manual instead of automated hyperventilation; (5) limiting lung inflations to a Pao of 20–25 cm H₂O during the hyperventilation (Morris, 2009); however, the volume was raised to 30 cm H₂O in the last two inflations in order to induce a robust PHA and ensure that no air leak occurred at the pPao; (6) monitoring the epigastric region by palpation between measurements which was critical; (7) delaying or spacing out raised volume maneuvers during peak sedation to allow swallowed air to migrate to the distal intestines; and (8) quickly aborting a lung inflation once any of the following occurred: (a) a characteristic low pitch sound indicative of esophageal air entry was heard or palpated by the investigator holding the infant's mandible; (b) a sluggish rise in the airway opening pressure or an early Pao plateau at a low pressure was noted in real time on the computer monitor screen; or (c) a steep linear rise in Pao which indicated upper airway obstruction often caused by the infant closing his/her mouth and swallowing repeatedly. Before resuming lung inflations, the closed mouth was re-opened, the airtight seal around the facemask was rechecked and the head was repositioned with the neck slightly extended (Mead, 1980; Motoyama, 1992; Morris, 1999b, 2009; Isono, 2006).

2.7. Expiratory flow-volume curves from V_{30}

Figure 4 demonstrates smooth passive (pEFV), passive-forced (pFEFV) and forced (FEFV) expiratory flow-volume (EFV) curves that generated the IC, jSVC and FVC, respectively, during a PHA from infants no. 4 (Fig. 4A) and 15 (Fig. 4B) who were 21.6 and 38.6 wks old, respectively. All expiratory flow-volume curves were aligned at V_{30} (TLC) in order to reveal their individual shape. When the FEFV curves were aligned along the descending

portion or end-expiration (not shown), flow limitation was evident (ATS/ERS Statement, 2005).

2.8. Statistical analysis

Data were expressed as arithmetic means with standard deviation (s.d.) and 95% confidence intervals (CI). Statistical analysis included the paired *t*-test to compare measured volumes and capacities. *p* values of less than 0.05 for a two-tailed test were regarded as significant. A dot plot showing the individual RV, FRC_{dyn}, FRC_{st}, IC, jSVC and FVC measurements obtained from each of the seventeen subjects was presented (Fig. 5) (Armitage and Berry, 1994). The intrasubject coefficient of variation (CV%) was computed for each variable. Mean values (s.d.) (95% CI) of the following derived variables were calculated for each infant: TLC, jTLC, fTLC, SVC, IRV and ERV. These means as well as variables from the best FEFV curve (ATS/ERS Statement, 2005) from all infants were presented as scatter plots against their respective age, body length, and weight measurements. The ratios of the FRC and the RV to total lung capacity were also computed. Regression lines were fitted to the data (Armitage and Berry, 1994). Linear regression equations for all variables versus the infant length are listed in Table 3. The bias and limits of agreement between the SVC-jSVC, jSVC-FVC, TLC-jTLC and jTLC-fTLC were calculated (Bland and Altman, 1986).

3. Results

A summary of results is presented in Table 2. Infant no. 7 woke up before an IC- FRC_{st} maneuver could be done and in three others only one maneuver was performed. However, the FRC_{st} was within 5% of the FRC_{dyn}, and the TLC was within 1–2% of the jTLC and fTLC. Therefore, they were entered in the analysis. In another infant, one jSVC that was within 10% of the FVC and SVC measurements was also included. Their inclusion did not skew the outcome (see below).

3.1. Subdivisions of lung volume at V₃₀

No more than 2–3 tries were needed to obtain at least two intrasubject FRC_{dyn}, IC, FRC_{st}, TLC, jSVC, RV, jTLC and FVC measurements within 5–10% (Fig. 5); the geometric means of CV% were 1.4, 1.9, 1.7, 1.1, 1.4, 1.5, 1.3 and 0.9, respectively. FRC_{dyn} and FRC_{st} measurements overlapped (*p*= 0.6420; paired *t*-test) (Morris, 2009) but neither did with the RV; their means were higher than mean RV (*p* < 0.0001; paired *t*-test, Figs. 5 and 6).

The dynamic and static lung volumes and capacities (Fig. 6) and the expiratory times of the IC and FVC (data not shown) exhibited body length (Table 3), weight and age dependence. The ratios of the RV and the FRC_{dyn} to total lung capacity decreased with increasing length (Fig. 7), weight and age (data not shown). Table 4 shows CILF data from infant no. 11 which demonstrates the interrelation between precisely measured and derived variables.

3.2. Analyses of recorded signals

The recorded signals during the IC-FRC_{st} and the jSVC-RV maneuvers were analyzed on the custom made system's computer; the aim was to confirm that the lung volume was raised to a Pao of 30 cm H₂O and, that after end-expiration when the slide valve switched the infant into the pure oxygen, the infant was in a PHA and the lungs were indeed at the elastic equilibrium volume level (Fig. 2A) and the RV (Fig. 2B), respectively (Morris, 1999b, 2009). Figure 3 demonstrates the raised volume RTC technique in infant no. 2. Note the early prominent peak of maximum flow (1978 ml/sec) at 2.505 sec, within 0.080 sec from the onset of the forced expiration. The ratio of the expired volume (26.96 ml) at peak

expiratory flow and FVC (693.6 ml) as percent ($V_{PEF}/\%FVC$) is 3.89 % (ATS/ERS Statement, 2005). Note that no volume was passively exhaled prior to activating the jacket.

The intrasubject number of raised volume RTC maneuvers (median, range) in the cohort was 6 (2 – 10). Using increasing jacket pressures, about 3–4 maneuvers were usually needed to achieve flow limitation (Fig. 4A) but two infants woke up unexpectedly after two maneuvers. Nevertheless, the lowest and highest intrasubject FVC from all tries were within 5% of each other in most infants and within 10% in the others. Actually in 12 infants at least two FVC measurements were within 0.1–3.0 ml of each other. Infant no. 15 (Fig. 4B) had fifteen raised volume maneuvers that did not affect subsequent FVC or other measurements.

The forced expiratory volume-time (FEV_t) and forced expiratory flows ($FEF_{\%}$) variables exhibited body length (Figs. 8 and 9; Table 3), weight and age dependence (data not shown). The $FEV_{0.4}/FVC$ and $FEV_{0.5}/FVC$ ratios as well as the rate constant between 50 and 75% of the FVC (RC_{50-75}) exhibited negative dependence with body length (Figs. 10 and 11; Table 5), weight and age (data not shown).

4. Discussion

In the present study, the support of our main hypothesis is illustrated in Table 4 which demonstrates the dual volume measurements from single maneuvers and the interrelation between the precisely measured and derived variables in infant no. 11.

The $jSVC$ and IC were reliable static volume measurements generated from V_{30} during the PHA. The mean FVC was insignificantly higher than mean $jSVC$ in 11/17 infants (most within 2%) which was ascribed to the methodological difference, automated versus manual ($p=0.9822$, Table 2; Figs. 2B, 3–6 and 12). Similarly, mean $jTLC$ and $fTLC$ were comparable in this healthy infant cohort ($p=0.9680$, Figs. 6 and 12; Table 2). The mean TLC was slightly lower (within 2–5%) than mean $jTLC$ ($p=0.0612$) and $fTLC$ ($p=0.0117$, Figs. 6 and 12; Table 2) in ten infants and lower than either one in three others. This physiologically insignificant difference was ascribed to very low end-passive expiratory flows for PNT detection when measuring the IC, rather than to a lower $aPao$ (Table 2; Figs. 2–6 and 12). As we also hypothesized, measured volumes and capacities were indeed dependent on the respective infant's anthropometric measurements (Fig. 6; Table 3).

The passive ($pEFV$) and the passive-forced ($pFEFV$) expiratory flow-volume (EFV) curves that generated the IC and $jSVC$, respectively, were quite reproducible (Fig. 4). Like the $FEFV$ curves, they could provide comparable variables such as the passive expiratory flows, expiratory times (Table 2) and timed expiratory volumes. These new variables could potentially be useful in studies aimed at tracking the lung growth and development as well as respiratory disorders affecting the elastic recoil of the respiratory system, including chest wall diseases.

4.1. Advantages of the technical aspects of the refined automated raised volume RTC

The FVC measurements were highly repeatable by our refined raised volume RTC (Figs. 5, 6 and 8). Moreover, the intrasubject mean FVC and $jSVC$ were comparable in our healthy infants. Both means were not smaller than mean SVC which indicated that the jacket placement did not limit chest wall expansion (Table 2; Figs. 5, 6 and 12) (Lum et al., 2002).

4.1.1. Automating raised volume RTC via the pressure transducer at the airway opening—The solid state pressure transducer (Morris, 1999b), which terminated the automated lung inflation at the exact $pPao$, exhibited an exceptional pressure linearity when tested in vitro ($r^2 = 1.0$). The pressure transducer was also placed closer to the airway

opening than the pressure-relief valve (Fig. 1) (Feher et al., 1996; ATS/ERS Statement, 2005). In addition, the release of pressure at any adjusted pressure level by the pressure-relief valve was found to be dependent on its spatial position and the bias airflow rate used (personal observations). Thus, the pressure transducer measured not only a reliable 'true' aPao reflective of the extent of lung inflation but also a P_{trans} that helped in determining whether or not the fastened jacket around the infant was tight (Fig. 3). Furthermore, the pressure transducer provided the investigator with crucial instantaneous information during the progress of lung inflation (see Section 2.6).

4.1.2. Actual airway opening pressure (aPao)—Raised volume RTC is primarily defined by lung inflation to a predetermined airway opening pressure (pPao) since a lower pressure is associated with a smaller FVC (Turner et al., 1995; Feher et al., 1996; Morris, 1999b; Lum et al., 2002; ATS/ERS Statement, 2005). However, a true aPao reflective of the extent of lung inflation is crucial and can only be ascertained by occluding the airway for 0.20 sec after terminating the inflating airflow and before activating jacket inflation (Turner et al., 1995; Morris, 1999b). For this reason, the aPao is quite different from maintaining a 'fixed' inflating airflow of 12 or 15–20 L/min until a Pao plateau at 30 cm H₂O and a zero flow are attained via a pressure relief valve before activating jacket inflation as reported in other studies (Feher et al., 1996; Jones et al., 2000; Goldstein et al., 2001; Lum et al., 2002a, 2002b, 2004; Ranganathan et al., 2002a, 2002b; Robin et al., 2004; ATS/ERS Statement, 2005). If the inflating airflow was high relative to the infant's size, the Pao plateau at V_{30} that an investigator observes in real time on the computer monitor screen may not have yet equilibrated with a 'lower' distal airways pressure. In fact, in the absence of a pneumatic circuit airleak, we have found out that a high inflating airflow relative to the infant size was invariably associated with a significant drop in aPao of about 2–4 cm H₂O below the pPao during the 0.2 sec airway occlusion. Consequently, a small FVC was generated (personal observations).

In the present study, aPao was more often very close rather than equal to 30.0 cm H₂O. The aPao was never higher than the pPao during a PHA (Fig. 3). We thought that attaining an exact 30.0 cm H₂O aPao was unrealistic because of the slow opening of previously collapsed distal small airways and the fact that the airways and lungs are distensible and do not conform to a single compartment model (Morris, 1999b; Lum et al., 2002a; ATS/ERS Statement, 2005; Stocks, 2006). Therefore, automated lung inflation was initiated before end-passive expiration of the last manual inflation. The aim was to enhance the equilibration of pressure throughout the distal airways since the proximal ones and the lungs were already partially distended by a positive end-expiratory pressure (Fig. 3) (Turner et al., 1995; Morris, 1999b; ATS/ERS Statement, 2005). In addition, the airflow rate was tailored to the infant's age and size. We used 5 and 12 L/min to generate the last automated inflation in the youngest and oldest, 8.6 and 119.7 weeks old, respectively. Consequently, an aPao close to 30.0 cm H₂O was easily attained which greatly reduced the variability in attained raised volumes at aPao. Thus, the precisely generated FVC also correlated well with the $jSVC$ and the SVC which were performed manually in our healthy infants (Tables 2–5; Figs. 4–6 and 12).

4.1.3. Minimizing technical/artificial flow transients in the FEFV curves—In the present investigation, the peak flow (PF), the smoothness of FEFV curves and the reproducibility of the FEF_{90} were enhanced (Fig. 4) by the following technical measures: (1) performing the anterior mandibular thrust (Morris, 2009) while keeping the infant's mouth open and the neck slightly extended; (2) placing the mini-balloon valve between the PNT and the Y adapter; (3) directing the bias airflow upwards toward the expiratory limb of the adapter, away from the PNT (Fig. 1), which minimized the noise in the flow signal baseline (Figs. 2–3); hence, the flow calibration of the PNT with and without the bias airflow was

virtually identical (personal observations); (4) automating raised volume RTC via the pressure transducer placed at the airway opening; (5) using two separate bias airflows instead of one which prevented gas turbulence within the PNT (Fig. 1) (see below) (6) halting the inflating airflow and occluding the airway for 0.20 sec once the pPao was attained (Turner et al., 1995; Morris, 1999b); and (7) maintaining the occlusion for only 0.05 sec after jacket activation (Morris, 1999b; ATS/ERS Statement, 2005); this short occlusion period not only minimized the volume of passively exhaled air prior to full jacket inflation but also facilitated the generation of a minimal P_{trans} because the jacket was not yet fully inflated (Fig. 3). Maintaining an insignificant P_{trans} (0–3 cm H₂O) virtually eliminated airleaks around the facemask (Morris, 1999b) and added a safety element to our technique. Moreover, flow transients' artifacts induced by glottic closure were tremendously reduced in the present study. In the FEFV curve, these flow transients often affected the FEF_% between PF and FEF₅₀ and rarely the FEF_{50–85} or FEF₉₀ (personal observations) (Figs. 4 and 9) (Morris, 1999b; Lum et al., 2002b; ATS/ERS Statement, 2005). Meanwhile, maximal expiratory flow was enhanced and flow limitation was achieved in the FEFV curves without startling the sleeping infant (Figs. 3, 4 and 9; Table 5). Studies which generated forced expiration from a low pPao of 20 cm H₂O had to use a longer airway occlusion period of 0.1 sec after jacket activation. Their aim was to generate a P_{trans} of at least 20 cm H₂O leading to an airway opening pressure of 40 cm H₂O in an attempt to achieve maximal forced expiration (Turner et al., 1995; Hayden et al., 1997; Linnane et al., 2008; Loland and Bisgaard, 2008).

In earlier reports, a single lung inflation-expiratory path was used during manually performed raised volume RTC with the PNT directly connected to the T-piece carrying the bias airflow (Feher et al., 1996; ATS/ERS Statement, 2005). The generated FEFV curves had significant artificial flow transients. These transients would affect the reproducibility of the forced expiratory flows (FEF_%) far more than the volume-time (FEV_t) variables (Feher et al., 1996; Morris, 1999b; Beardsmore et al., 2001; Goldstein et al., 2001; Lum et al., 2002a, 2002b, 2006; Ranganathan et al., 2002b; ATS/ERS Statement, 2005; Merkus et al., 2005; Modl and Eber, 2005; Stocks, 2006).

4.2. Comparisons of variables with those of previous studies

Using the prediction equations of the respective study, estimates of variables were generated at 60 and 75 cm of infant body length for comparisons between previous studies and the present one (Table 5). The observed differences could be ascribed to methodological and population differences.

Thorsteinsson et al. (1994) reported a mean TLC of 62.2 ml/kg at V₃₀ as the sum of FRC measured by the sulfur hexafluoride multiple-breath washin/washout and the volume above FRC in 23 infants aged (range) 0.1–2.6 years and measuring 47–91 cm long during anesthesia and muscle paralysis. Using the quadratic regression equation that best fitted these infants' data, we estimated values of TLC at 60 and 75 cm of infant length to be 288.6 and 597.6 ml, respectively, which were comparable to ours (Table 5; Fig. 6) (Thorsteinsson et al., 1994; Castile et al. 2000).

Castile et al. (2000) reported a mean TLC of 60.1 ml/kg as the sum of RV and FVC in 22 infants aged 3–120 weeks. The RV was obtained by subtracting the ERV from FRC_{pleth}. The ERV was measured as the difference between the lung volume at end-forced expiration and the point at which a stable end-tidal expiratory level was re-established. However, the ERV was the most variable measurement in the study (CV, 13.5 ± 8.9%) (Castile et al., 2000), apart from the fact that the FRC_{pleth} measurement might potentially be inaccurate in infants (Hammer et al., 1998; Hülskamp et al., 2003; Broughton et al., 2006, 2007; Morris, 2009; Poorisrisak et al., 2009). Indeed, Hülskamp et al. (2003) reported FRC_{pleth}

measurements which accounted for the deadspace of the facemask among other volume errors (Morris, 1999c). The authors concluded that previous equations had overestimated FRC_{pleth} and cast doubt on the physiologic presence of trapped gas in healthy infants. Thus, the following are comparisons of estimated variables at 60 and 75 cm of infant body length by Castile et al. (2000) versus our study (Table 5): (1) ERV was about 74 and 120% higher than ours; (2) FRC_{pleth} was 13 and 30% higher than our FRC_{dyn} ; (3) RV was 22.5% higher and 8% lower than our RV measured by MBNW, respectively; and (4) TLC was within 10% of our $jTLC$ and $fTLC$ and just above 10% of our TLC. Hence, the RV measurements by Castile et al (2000) would be affected by the inherent variability of the two primary measurements, namely the ERV and FRC_{pleth} . In the present study, the intrasubject RV and FRC measurements by MBNW were very precise and did not overlap. Therefore, the ERV, which is the difference between mean values, was a highly repeatable measurement (Figs. 5 and 6; Tables 2–5) (Morris, 1999b, 2009). In agreement with our recent report, the findings of no difference between intrasubject mean FRC_{dyn} and FRC_{st} along with the high precision and overlap of measurements (Fig. 5; Tables 2 and 5) cast significant doubt on the traditional physiology of air trapping in healthy infants' lungs (Morris, 2009).

In the present study, measuring the TLC in three different ways would be useful when testing infants who have an underlying respiratory dysfunction (Figs. 6 and 12). Thus, in infants with airway obstruction, a small FVC would be generated because of increased flow limitation and air trapping. Consequently, the $fTLC$ would be smaller than the TLC and $jTLC$. In addition, the FRC/TLC and RV/TLC ratios (Fig. 7) could help in assessing the degree of hyperinflation (Hammer et al., 1998; Castile 2004). In restrictive lung disease, the three measurements of total lung capacity would be equally decreased.

The range of jacket pressures used during raised volume RTC by Jones et al. (2000) was 40–120 cm H₂O. Despite using considerably lower mean (s.d.; range) jacket pressures in our study than Castile et al. (2000), 52.4 (8.4; 39–75) versus 81.1 (20.2; 49–138) cm H₂O, the peak of maximum flow was consistently slightly higher in our FEFV curves (Tables 2 and 5; Fig. 9). We ascribed the difference to our raised volume RTC technique of keeping the mouth slightly open and performing an anterior jaw thrust while keeping the neck slightly extended. Consequently, the increased upper airway resistance of the sedated infant, which would choke the peak expiratory flow, was drastically reduced during the forced expiration (Green et al., 1974; Mead, 1980; Hershenson et al., 1984; Motoyama, 1992; Isono, 2006; Morris, 2009). In the present study, the FVC was comparable to Jones et al. (2000) and Castile et al. (2000) though slightly higher (16%) at 75 cm infant length by Castile et al. (2000) (Figs. 6 and 8; Table 5). In the study by Jones et al. (2000), flows at low lung volumes tended to be slightly lower than the present study (Table 5; Fig. 8). In their study, 30% of infants were exposed to tobacco smoke during pregnancy, which resulted in lower forced expiratory flows in these infants, and 50% were exposed postnatal (Jones et al., 2000; Hofhuis et al., 2003; Stocks and Dezateux, 2003; Milner et al., 2007; Wigle et al., 2007).

Consistent with previous reports, variables from the best FEFV curve (Figs. 8–11; Tables 3 and 5) were related to the respective infant's length (Jones et al., 2000; Castile et al., 2000), and age (Jones et al., 2000). In the present study they also exhibited weight dependence (not shown). The $FEV_{0.5}$ and $FEV_{0.5}/FVC$ ratio by Jones et al. (2000) were comparable to the present study (Table 5; Figs. 8 and 10). Moreover, when the FVC and $FEV_{0.5}$ from our 17 infants were plotted on the scatter plot of collated multicenter data (ATS/ERS Statement, 2005), they fitted well within the data (data not shown).

The rate constant for lung emptying during forced expiration decreased with infant body length whether measured as the ratios of $FEV_{0.4}/FVC$ or $FEV_{0.5}/FVC$ or as the slope between 50 and 75% of the FVC (RC_{50-75}) (Figs. 10 and 11; Table 5). These findings,

which indicated that the lung volume increased more rapidly than airway caliber in early life, are consistent with the concept of dysanaptic lung growth, namely, the dissociation between the growth of the lung parenchyma and the airways (Green et al., 1974; Bryan and Wohl, 1986; Tepper et al., 1999; Jones et al., 2000). Our mean RC_{50-75} was comparable to Tepper et al. (1999) (Table 2). The ratios of the RV and the FRC to total lung capacity also decreased with increasing infant length (Fig. 7). The decline could be ascribed to a more rapid increase in the vital and inspiratory capacities, which represent the exchangeable lung volume, than the RV and FRC, respectively (Fig. 6) (Gaultier et al., 1979; Castile et al., 2000). Thus, from an infant length of 60 to 75 cm, the estimated RV, $jSVC$, FRC and IC in our study increased by 87, 106, 82 and 112%, respectively (Table 5). The FRC_{pleth}/TLC and RV/TLC ratios by Castile et al (2000) were comparable to ours (Table 5; Fig. 7).

In the forced deflation technique, the intubated airway is suddenly exposed to negative pressure, resulting in rapid lung deflation from a raised volume to an inspiratory pressure of +40 cm H_2O (V_{40} or TLC_{40}) (Motoyama, 1977; Hammer and Newth, 2005). At V_{30} , the reported mean FVC by forced deflation was 40.7 ml/kg, which was comparable to ours (Table 2); however, it increased to 51.2 ml/kg at V_{40} (Hammer and Newth, 1996). Hammer et al., (1998) reported passive expiration from V_{40} that generated comparable TLC measurements either by MBNW (TLC_{N_2}) or calculated as the sum of FRC measured by MBNW (mean, 23.3 ml/kg) and the inspiratory capacity (mean, 42.7 ml/kg) measured by a PNT. von Ungern-Sternberg et al. (2009) reported measurements by forced deflation and passive expiration from V_{40} in 100 healthy infants aged 6–258 weeks. At 60 and 75 cm of infant length, the estimated IC and FVC were higher than the present study (Table 5). The differences were ascribed to two potential reasons: (1) raising the lung volume to V_{40} instead of V_{30} ; and (2) paralysis of intercostal muscles and diaphragm which increases chest wall compliance and also decreases the resting lung volume (De Troyer et al., 1979; Hammer and Newth, 1996; Hammer et al., 1998; von Ungern-Sternberg et al., 2006, 2009; Morris, 2009).

Contrary to raised volume RTC, flow limitation by forced deflation can only be assessed at very low lung volumes, the FEF_{75} and FEF_{90} . However, the FEF_{75} and FEF_{90} do not routinely characterize levels of airway dysfunction as well as mid-expiratory flows do. In fact, the FEF_{50} is a useless index of airway function by forced deflation because it is affected by the endotracheal tube (Motoyama, 1977; Hammer and Newth, 1996, 1997, 2005; von Ungern-Sternberg et al., 2009). The FEF_{75} and FEF_{90} generated by forced deflation were significantly lower than those generated by raised volume RTC from V_{30} , including the present study (Table 5; Fig. 9). von Ungern-Sternberg et al. (2009) have postulated three reasons for this unexpected difference: (1) flows are measured at lower volumes since the FVC is generated from V_{40} instead of V_{30} ; (2) potential effect of the endotracheal tube; and (3) difference in generating the FEFV curve, namely the forced deflation in heavily sedated and paralyzed infants versus RTC in non-intubated and non-paralyzed infants.

4.3. Advantages of comprehensive integrated spirometry at V_{30}

By combining in single maneuvers the volumes integrated from PNT flow measurements with those measured indirectly by MBNW, the unique design of the T-valve enabled accurate dual volume measurements at V_{30} to be performed with interdependence between measured volumes. Hence, the intrasubject analysis of the interrelation between variables and interpretation of data was enhanced by revealing physiological harmony or implausible differences between static and dynamic lung volumes. Thus, a quality assurance element was incorporated into the CILF that resulted in reliable physiological, technical and clinical interpretation of the variability in the data in an algorithmic fashion (Tables 4 and 5) (personal observations): For example, when measuring $jSVC$ and RV within a single maneuver in a healthy infant: (1) a relatively large RV with a small $jSVC$ along with an

acceptable j_{TLC} might indicate that a low jacket pressure (P_j) was used; (2) a significantly smaller j_{SVC} than SVC and a smaller j_{TLC} than TLC along with an acceptable RV might point to a tightly placed jacket around the infant that had limited lung inflation; in addition, a small FVC and f_{TLC} would be obtained. Switching the infant prematurely into pure O_2 before end-passive expiration from V_{30} would result in a small IC and a large FRC_{st} (Morris, 2009) despite an acceptable TLC. A small FVC could result from a very loosely applied jacket generating inadequate RTC or a tightly placed one that limited lung inflation or gastric distension or a combination of these factors. Other examples that would alert the operator to a specific error in a measurement or the need to redo a maneuver: an $IC > FVC$ or j_{SVC} , $FVC > j_{SVC}$, $RV \geq FRC$, etc. A higher peak flow (PF) in the passive (pEFV) than in the forced (FEFV) expiratory flow volume curves or a progressive decline in PF in the FEFV curves despite increasing jacket pressures indicated the need to re-open the mouth before resuming raised volume RTC. A higher intrasubject PF was often noted in the passive-forced (pFEFV) than in the passive (pEFV) expiratory flow-volume (EFV) curves that generated the j_{SVC} and IC, respectively (Fig. 4). The difference was ascribed to the weight of the jacket and attached hose rather than a tight jacket placement.

In the present study, the raised volume maneuvers have not caused significant epigastric distension that would have led to progressive decrease in IC, FVC or j_{SVC} or affected other measurements (Figs. 4–12). Reported raised volume RTC techniques, which used a ‘fixed’ inflating airflow of 12 or 15–20 L/min and kept the lungs inflated at a Pao plateau of 30 cm H_2O via a pressure-relief valve until a zero flow was attained, would likely cause significant aerophagia (Beardsmore et al., 2001; Goldstein et al., 2001; Lum et al., 2004, 2006; Robin et al., 2004; ATS/ERS Statement, 2005; Modl and Eber, 2005). It was reported that ventilating infants via the oral route may or may not enhance the induction of gastric insufflation (Segedin et al., 1995; Wilson-Davis et al., 1997).

Taken together, CILF incorporates powerful intrinsic quality control parameters. CILF would enable the investigator to gain valuable algorithmic insights into intrasubject physiological or pathophysiological factors that might affect measured variables. In addition, CILF allows a systematic evaluation of potential effects of critical technical elements such as the sequence of tests, influence of sedation, repeated lung inflations (Morris, 2009), jacket placement and repeated RTC on various maneuvers and findings.

4.4. Study limitations and future directions

The present methodology study was limited by the small number of subjects made of boys and girls from two races, Caucasians and blacks.

Respiratory diseases such as asthma, bronchopulmonary dysplasia and cystic fibrosis, all of which are associated with airway obstruction, air trapping, abnormal flow limitation and lung volume are present in early life. Thus, rather than seeking the best test (Frey, 2001), the CILF measures all subdivisions of lung volume at V_{30} and multiple physiological parameters, including those of the best FEFV curve, that are relevant to the underlying pathophysiology. Therefore, CILF would readily discriminate between health and disease and investigate in-depth the dysfunction in various respiratory diseases and disorders (Morris, 1999b, 2009; Stocks et al., 2007). Larger studies on healthy infants and those with lung disease are needed to generate normative data and regression equations and explore the clinical usefulness of CILF and the new variables. CILF data from healthy infants would be valuable in prospective studies aiming at exploring the impact of genetic, prenatal and postnatal environmental factors or exposures on lung growth, development and function (Hofhuis et al., 2003; Stocks and Dezateux, 2003; Milner et al., 2007; Piippo-Savolainen and Korppi, 2008; Wigle et al., 2007; Carlsen et al., 2009; Castro et al., 2009; Martinez, 2009).

5. Conclusions

We have combined precise and accurate volume measurements integrated from the PNT flow signal with indirectly measured volumes by MBNW within single maneuvers in a group of healthy infants. Therefore, a novel, conceptual and physiologically-integrated approach that emphasizes a CILF for measuring static and dynamic lung volumes and capacities at V_{30} was developed. Several new precisely measured and derived variables are described which were obtained with and without the squeeze jacket fastened around the infant such as the inspiratory (IC) and slow vital capacities ($\dot{V}_{SVC}$ and SVC). Repeatable measurements of the total lung capacity, which were obtained in three different ways, were comparable in healthy infants. Precise and comparable measurements of the functional residual capacity were also obtained with two different methods (Morris, 2009). Variables were dependent on body length, weight, and age. Innovative single maneuvers with dual volume measurements at V_{30} are valuable in the rapidly growing infant population because of the limited and unpredictable period of sleep-induced sedation. Without causing significant aerophagia, a refined automated raised volume RTC technique is described which generated highly precise FVC measurements. The smooth FEFV curves had a prominent peak of maximum flow and flow limitation was easily achieved. A 'true' actual airway opening pressure (aPao) is also described that was closely related to the generated FVC. Single maneuvers with dual volume measurements from V_{30} could similarly be automated which would facilitate the execution of CILF. CILF would enable intra- and inter-laboratory comparisons of data. Hence, CILF would facilitate the standardization of testing as well as the tracking of lung function in multicenter studies through the first three years of life and beyond (Stocks et al., 2000; Beardsmore et al., 2007; Morris, 2009).

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Glossary of Abbreviations*

CILF	comprehensive integrated lung function (testing)
ERV	expiratory reserve volume
FEF _%	forced expiratory flow at fixed proportions of FVC (FEF ₂₅ , FEF ₅₀ , FEF ₂₅₋₇₅ etc.)
FEFV	forced expiratory flow volume (curve); it generates FVC
FEV _t	forced expiratory volume-time; FEV _{0.4} or 0.5 expired volume during the first 0.4 or 0.5 sec after the start of forced expiration
FRC _{dyn}	<i>dynamic</i> functional residual capacity (FRC); MBNW is initiated at or close to end-tidal expiration
FRC _{st}	<i>static</i> functional residual capacity; MBNW is initiated after end passive expiratory switching of the inspired gas from room air to 100% O ₂ during a PHA
FRC _{Pleth}	FRC measured by plethysmography

FVC	forced vital capacity
IC	inspiratory capacity; generated by a complete passive expiration from V_{30} during a PHA
IRV	inspiratory reserve volume; <i>equals IC minus Tidal volume</i>
MBNW	multiple-breath nitrogen (N_2) washout
Pao	airway opening pressure
pPao	predetermined Pao; lung volume is raised to a pPao value entered on computer which once attained as sensed by the pressure transducer placed at the airway opening, lung inflation is automatically halted
aPao	actual Pao; computed as ensemble average of Pao during a 0.2 sec airway opening occlusion after halting the inflating airflow and before activating jacket inflation.
pEFV	passive expiratory flow volume (curve); it generates IC
PF	peak flow
pFEFV	passive-forced expiratory flow volume (curve); it generates $jSVC$
Pj	jacket pressure
P_{trans}	pressure transmission; number of cm H_2O above the aPao plateau generated by jacket inflation (RTC) during an airway occlusion
PNT	pneumotachometer
PHA	post-hyperventilation apnea
RTC	rapid thoracoabdominal compression
RV	residual volume measured by MBNW
SVC	slow vital capacity; <i>equals TLC minus RV</i>
$jSVC$	SVC generated by activating jacket (j) inflation late during passive expiration from V_{30} during a PHA
TLC	total lung capacity; <i>equals IC plus FRC_{st} (or FRC_{dyn})</i>
$jTLC$	<i>equals $jSVC$ plus RV</i>
$fTLC$	<i>equals FVC plus RV</i>
V_{30} or V_{40}	raised lung volume to a Pao of 30 or 40 cm H_2O

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Figure 1- T-valve
MG Morris

Figure 1.

T-Valve Unit. Side views depict the path (arrows interconnected by a dotted line) through the T-valve of air (Fig. 1A) and, after activating the slide valve piston, the path of O₂ (Fig. 1B) in and out of the infant's airway. The Y adapter is connected to the mini-balloon valve when measuring the IC (Fig. 2A) with the FRC_{st}, or the jSVC (Fig. 2B) with the RV and during raised volume RTC (Fig. 3). The infant is hyperventilated by intermittently occluding the expiratory limb of the Y adapter until a PHA is induced (Fig. 1A). Lung volume is raised to a Pao plateau set at 30 cm H₂O by the pressure relief valve. Note that the infant breathes in and out of the PNT when measuring the IC and jSVC but not after the slide valve switches him/her into O₂ (Fig. 1B) to measure the FRC_{st} and RV, respectively. The long parallel dotted lines point to the connection of the slide valve outlet port to the N₂ washout circuit outlined in the background (Morris, 1999b). Fig. 1C demonstrates the pneumatic circuit delivering airflow via the PNT to the airways (dotted line arrow exiting the facemask) while the mini-balloon valve's balloon is inflated during automated raised volume RTC.

Figure 2.

Measurement of: (A) IC and FRC_{st} (squeeze jacket unfastened); (B) $jSVC$ and RV. Examples of trace of flow, volume and Pao , and in (B) of Pj , of the last manual lung inflation from infant no.1; inspiration is positive and expiration is negative. Note that the infant breathes in and out of the PNT when measuring the IC or $jSVC$ but not after the slide valve switches him/her into the O_2 bias flow to measure the FRC_{st} or RV. A PHA was induced. As the lung volume is raised, Pao rises to a plateau set at 30 cm H₂O by the pressure relief valve. Release of the expiratory thumb occlusion initiates the passive expiratory flow:

(A) Flow signal is integrated to produce volume (IC). The expiratory time (t_{IC}) is 1.770 sec. Note that both Flow and Pao are at zero during the post-expiratory apnea indicating that the elastic equilibrium volume of the respiratory system is attained. At 9.825 sec, an abrupt upward shift in Pao to 0.54 cm H₂O and the disappearance of tiny peaks in the flow trace baseline indicate the infant is switched into O₂. A negative deflection in the Pao trace that starts at 11.70 sec signals the resumption of inspiration.

(B) Before end-passive expiration, jacket activation at 1.070 sec generates a positive small sharp peak (partial forced expiration) on the expiratory flow limb and a tiny rise in Pao which rapidly returns to zero. The expiratory time (t_{jSVC}) is 1.980 sec. Flow signal is integrated to produce volume (j_{SVC}). At 2.85 sec, an abrupt upward shift in the Pao trace zero baseline to 0.66 cm H₂O indicates the infant is switched into O₂, and a zero Flow with a raised Pj plateau to 55.5 cm H₂O indicates chest compression (lungs are at RV). A negative deflection in the Pao trace that starts at 15.18 sec signals the resumption of inspiration.

Figure 3.

Raised volume RTC. An example of trace of flow, volume, Pao and Pj of the last (automated) lung inflation which starts at 1.550 sec during early expiration of the previous (last) manual inflation from infant no. 2; inspiration is positive and expiration is negative. A PHA was induced. As the lung volume is raised, Pao rises to a preset (pPao) value of 30.6 cm H₂O at 2.220 sec. The inflating airflow is then (automatically) halted and the airway simultaneously occluded for a period of 0.20 sec which ends at 2.420 sec. Note a 'true' zero flow and volume plateaus and that the pPao drops to a 'true' actual (aPao) level of 29.7 cm H₂O during this 0.20 sec period. Note that jacket inflation begins at 2.42 sec but the airway occlusion continues for another 0.05 sec. Hence, the rising Pj causes a second transient tiny rise (P_{trans}, 2.6 cm H₂O) in aPao to 32.3 cm H₂O at 2.48 sec. The occlusion is then

terminated and forced expiration starts. Forced expiration is completed at 3.890 sec before the end of the Pj plateau (64.3 cm H₂O). The expiratory time (*t*FVC) is 1.465 sec. The PHA lasted for 12.56 sec after end-expiration (not shown).

Figure 4.

Representative expiratory flow-volume (EFV) curves. Passive (pEFV), passive-forced (pFEFV) and, using repeated raised volume RTC with increasing jacket pressures, the forced (FEFV) EFV curves from a lung volume raised to an airway opening pressure of 30 cm H₂O (V_{30}) generated the IC, j SVC and FVC, respectively from infants no. 4 (A) and 15 (B). All curves are aligned at V_{30} (TLC). The abrupt increase in flow close to the end of the pFEFV curves is caused by late jacket activation which generates a (partial) forced expiration to residual volume producing the j SVC. Note the smoothness of the flow-volume curves and the high precision of measured variables. Note that PF is higher in the FEFV than the pEFV and pFEFV curves.

Figure 5- Dot Plot
MG Morris

Figure 5.

A dot plot showing individual FRC_{dyn} , FRC_{st} , IC, $jSVC$, RV and FVC measurements (ml) obtained from the 17 infants. RV and FRC were corrected for the mask dead space and converted to BTPS. FRC_{dyn} was also corrected for the switching error above FRC. Note the following: (1) lack of overlap between RV and FRC (2) overlap between FVC and $jSVC$ and between FRC_{st} and FRC_{dyn} ; and (3) high precision of measurements: Note that infant no. 4 had two FRC_{st} : 144.1 and 143.5; no. 6 had three $jSVC$: 161.1, 160.0 and 160.1; no. 9 had two FRC_{st} : 215.7 and 215.1 as well as two RV: 182.8 and 182.8; no.12 had two $jSVC$: 422.1 and 422.4; no. 15 had three RV: 163.2, 166.4 and 166.4 ml.

Figure 6. Mean values of tidal volume (V_T), RV, FRC_{dyn} , FRC_{st} , ERV, IC, IRV, TLC, SVC, $jSVC$, FVC, $fTLC$ and $jTLC$ from each infant along with regression lines plotted against the respective infant body length, weight and age. The two regression lines of the $fTLC$ and $jTLC$, FVC and $jSVC$, as well as FRC_{dyn} and FRC_{st} overlapped, respectively; therefore, only one line for each pair of these variables was plotted.

Figure 7.

Ratios of the RV and FRC_{dyn} to the total lung capacity that was measured in three different ways from each infant along with the regression lines are plotted against the respective infant length and exhibiting negative dependence (* slope, Y-intercept).

Figure 8.

Forced expiratory volume-time (FEV_t) variables and FVC of the best FEFV curve from each infant along with regression lines are plotted against the respective infant length (* slope, Y-intercept).

Figure 9. Peak flow (PF) and forced expiratory flows (FEF_%) of the best FEFV from each infant along with regression lines are plotted against the respective infant length.

Figure 10.

Ratios of FEV_{0.4}/FVC and FEV_{0.5}/FVC of the best FEFV curve from each infant along with regression lines are plotted against the respective infant length and exhibiting negative dependence (* slope, Y-intercept).

Figure 11.

The rate constant between 50 and 75% of the FVC (RC_{50-75}) from the best FEFV curve from each infant and the regression line are plotted against the respective infant length and exhibiting negative dependence (* slope, Y-intercept).

Figure 12.

Bland-Altman plots showing the distribution of the differences between the following: (a) SVC and jSVC; (b) jSVC and FVC; (c) TLC and jTLC; (d) jTLC and fTLC as percent of their respective average. In each panel the horizontal solid line represents the mean % difference and the broken lines the 95% limits of agreement of the observed % differences.

Table 1

Data of Study Subjects

Subject no.	Sex & Race *	Age (weeks)	Length (cm)	Weight (kg)
1	MC	80.7	87.1	11.71
2	MC	119.7	95.3	12.35
3	FC	27.1	64.3	6.25
4	MC	21.6	66.3	7.78
5	FC	29.1	65.5	6.70
6	MC	8.6	58.9	5.77
7	FC	26.4	68.0	7.40
8	FB	77.6	82.9	11.08
9	MC	59.1	77.2	8.86
10	FB	22.3	69.1	8.59
11	FC	44.7	74.3	8.99
12	MB	48.3	79.6	10.27
13	FC	13.6	60.0	6.08
14	FC	42.6	72.5	9.01
15	MC	38.6	72.0	9.27
16	MC	98.1	85.4	11.48
17	MC	36.6	73.7	10.18

* M, male; F, female; C, Caucasian; B, Black;

Table 2

Lung volumes and capacities^a (ml/kg)^b at raised lung volume (V_{30}) and ratios of the FRC and RV to total lung capacity and the rate constant for forced expiration

FRC _{dyn}	21.2 (2.9) (19.7 to 22.7) ^c
FRC _{st}	21.2 (3.0) (19.6 to 22.8) ^c
IC	36.7 (7.0) (33.0 to 40.4)
<i>t</i> IC (s)	1.749 (1.340 – 2.660) ^{d, e}
TLC	57.8 (9.3) (52.8 to 62.8) ^f
<i>j</i> SVC	40.7 (6.8) (37.2 to 44.2) ^g
<i>t_j</i> SVC (s)	1.886 (1.360 – 2.385) ^{d, e}
RV	18.1 (3.1) (16.6 to 19.7) ^c
P _j (cm H ₂ O)	56.9 (6.5) (53.6 to 60.3)
<i>j</i> TLC	58.7 (9.6) (53.6 to 63.8) ^f
FVC	40.7 (7.0) (37.1 to 44.2) ^{g, h}
<i>t</i> FVC (s)	1.354 (0.870 – 1.915) ^{d, e}
P _j (cm H ₂ O)	52.4 (8.4) (48.6 to 56.7)
aPao (cm H ₂ O)	29.4 (0.4) (29.2 to 29.6)
<i>i</i> TLC	58.8 (9.2) (54.0 to 63.5) ^f
SVC	39.9 (6.9) (36.2 to 43.6) ^g
V _T	10.2 (1.2) (9.6 to 10.8)
IRV	24.9 (6.4) (20.3 to 29.5)
ERV _{dyn}	3.01 (1.3) (2.38 to 3.8) ⁱ
ERV _{st}	3.2 (1.3) (2.5 to 3.8) ⁱ
FRC _{dyn} /TLC	0.3663 (0.03196) (0.3493 to 0.3833) ^j
FRC _{dyn} / <i>j</i> TLC	0.3637 (0.03269) (0.3468 to 0.3805) ^j
FRC _{dyn} / <i>i</i> TLC	0.3635 (0.03313) (0.3465 to 0.3805) ^j
RV/TLC	0.3117 (0.03294) (0.2941 to 0.3292) ^j
RV/ <i>j</i> TLC	0.3092 (0.02820) (0.2947 to 0.3237) ^j
RV/ <i>i</i> TLC	0.3094 (0.03290) (0.2925 to 0.3263) ^j
RC _{50–75}	4.250 (1.388) (3.536 to 4.964) ^k

^a See Glossary of Abbreviations; *t*, time in seconds; *t*IC, *t_j*SVC, *t*FVC are the expiratory times of the respective volumes; V_T, tidal volume; RC_{50–75}, rate constant for forced expiration

^b Mean (standard deviation) (95% Confidence Interval)

^c were comparable ($p = 0.6420$) and both higher than RV ($p < 0.0001$) FRC_{dyn} and FRC_{st}

^d Difference between *t*IC and *t_j*SVC was statistically insignificant ($p = 0.1805$); however, both were longer than *t*FVC ($p < 0.0001$). Note that *t_j*SVC varies with the timing of jacket activation during the passive expiration from V₃₀.

^e Median (range)

^fTLC was slightly lower than jTLC ($p=0.0612$) and fTLC ($p=0.0117$); jTLC and fTLC were comparable ($p=0.9680$)

^gStatistically insignificant difference from FVC ($p=0.9822$) but slightly higher than SVC ($p=0.0358$)

^hFrom the best forced expiratory flow-volume curve (ATS/ERS Statement, 2005)

ⁱExpiratory reserve volume (ERV) was computed as the difference between the RV and either FRC_{dyn} (ERV_{dyn}) or FRC_{st} (ERV_{st}). Difference was statistically insignificant ($p=0.6030$)

^jDifference between the ratios of FRC_{dyn} and the RV to total lung capacity was statistically significant whether the ratio's denominator was the TLC, fTLC or jTLC ($p < 0.0001$).

^k $RC_{50-75} = (FEF_{50} - FEF_{75}) / (FEV_{50} - FEV_{75})$

Table 3Linear regression equations for volumes and capacities and FEF_% versus infant height

Volumes and Capacities ^a	Slope	Y-Intercept	r ²
FRC _{dyn}	5.957	-246.5	0.9273
FRC _{st}	6.071	-255.0	0.9327
IC	12.47	-581.0	0.9253
TLC	18.60	-840.1	0.9482
jSVC	13.45	-617.3	0.9530
RV	5.335	-228.5	0.9162
jTLC	18.81	-847.5	0.9588
FVC ^b	13.36	-610.6	0.9251
fTLC	18.72	-841.2	0.9445
SVC	13.03	-593.7	0.9299
V _T	2.112	-65.06	0.8815
IRV	10.20	-505.3	0.9206
ERV	0.6251	-18.40	0.1952
FEF _% variables ^b			
PF	29.80	-773.7	0.6629
FEF ₂₅	24.16	-721.7	0.7270
FEF ₅₀	16.76	-488.8	0.6930
FEF ₂₅₋₇₅	17.00	-574.3	0.7359
FEF ₅₀₋₈₅	12.34	-466.6	0.7210
FEF ₇₅	11.61	-473.2	0.7178
FEF ₈₅	6.327	-231.1	0.6026
FEF ₉₀	4.456	-164.1	0.5484

^a See Glossary of Abbreviations^b From the best FEFV curve (ATS/ERS Statement, 2005)

Table 4

Comprehensive integrated spirometric measurements^a from Infant no. 11. Female Caucasian aged 44.7 wks; length, 74.3 cm, weight, 8.99 kg; sleep duration, 147 min; Chloral hydrate, 740 mg p.o.

T_{est}^b	FRC _{dyn}	T_{est}^b	FVC	aPao	fFVC	Pj	tj	IC	T_{est}^b	fIC (s)	FRC _{st}	TLC
3	189.2	16	354.9	29.7	1.615	37.7	2					
5	192.2	17	351.2	29.7	1.605	45.7	2					
7	184.2	20 ^c	353.1	29.4	1.530	50.6	2.1					
23 ^d	194.3											
Mean (s.d.) [*]	190.0 (4.4)											
T_{est}^b	jSVC	t_j^{fSVC} (s)	RV _{N2}	jTLC	Pj	tj						
10	345.3	1.805	158.7	504.0	51.8	2		298.5	2.120	186.6	485.1	
12	348.2	1.980	159.2	507.4	60.1	2		313.2	1.940	197.8	511.0	
								318.3	2.270	186.0	504.3	
Mean (s.d.)	346.8 (2.1)	1.893 (0.124)	159.0 (0.4)	505.7 (2.4)			Mean (s.d.)	310.0 (10.3)	2.110 (0.165)	190.1 (6.7)	500.1 (13.4)	
Mean (s.d.) (95% Confidence interval) V _T = 84.5 (4.34) (82.2 to 86.8) ^e												
Derived volumes and capacities at V₃₀^f												
ERV = FRC _{dyn} or FRC _{st} - RV = {190.0 or 190.1} minus 159.0; ERV = 31.1												
• SVC = TLC - RV _{N2} = 500.1 - 159.0 = 341.1												
• IC = jTLC - FRC _{dyn} = 505.7 - 190.0 = 315.7 or												
= iTLC - FRC _{dyn} = 512.1 - 190.0 = 322.1												
• IRV = IC - V _T = 310.0 - 84.5 = 225.5 or												
= jTLC - (FRC + V _T) = 505.7 - (190.1 + 84.5) = 231.1												
= iTLC - (FRC + V _T) = 512.1 - (190.1 + 84.5) = 237.5												
• TLC = IC + FRC _{dyn} = 310.0 + 190.0 = 500.0												
• fTLC = FVC + RV _{N2} = 353.1 + 159.0 = 512.1												
• RV = TLC - FVC = 500.1 - 353.1 = 147.0 or												
= TLC - jSVC = 500.1 - 346.8 = 153.3												

^aSee also Glossary of Abbreviations; t, time in seconds; tj, time in seconds; fTLC, fFVC are the expiratory times of the respective volumes; fIC, fSVC, fFVC are the expiratory times of the respective volumes; tj, jacket compression time; RV_{N2}, RV measured by MBNW; V_T, tidal volume

^b Similar test maneuvers were grouped together with their actual sequence number shown. At least two measurements within 10% of each other were obtained. Note that only 2–3 tries were needed to attain this precision; Mean (s.d.). Volumes are in ml, pressures, in cm H₂O, and time, in seconds. Measured FRC and RV were converted to BTPS.

^c From the best forced expiratory flow volume curve. Five RVRTC were performed and flow limitation was achieved (ATS/ERS Statement, 2005).

^d Note that repeated RVRTC did not affect subsequent FRC_{st} or FRC_{dyn} in tests no. 23, 25, 27. Repeat MBNW did not affect measured volumes (Morris, 1999b, 2009).

^e Sixteen epochs of tidal breathing, 20 sec each, were recorded throughout the testing.

^f Note that each volume or capacity was derived from two or more variables that each had been measured with a different maneuver or test. Note that individual derived variables are within 10% of comparable measured or derived ones. Note that measurements of total lung capacity obtained in three different ways, TLC, jTLC and fTLC, are comparable in this healthy infant. Note also that jTLC and fTLC are not lower than TLC which indicates that the jacket placement did not restrict lung inflation.

Table 5

Comparisons of estimates of variables from the FEFV curve and fractional lung volumes from the present study with those from other studies^a

Infant length		60 cm		75 cm					
Variables	Our Study	Castile et al., 2000	Jones et al., 2000	von Ungern-Sternberg et al., 2009	Our Study	Castile et al., 2000	Jones et al., 2000	von Ungern-Sternberg et al., 2009	
PF	1014.3	958.9	<i>b</i>	-	1461.3	1364.1	-	-	
FEF ₂₅	727.9	752.8	-	-	1090.3	1063.6	-	-	
FEF ₅₀	516.8	460.9	464.6		768.2	779.2	706.4		
FEF ₂₅₋₇₅	445.7	413.9	407.1		700.7	724.1	641.0		
FEF ₇₅	223.4	220.6	204.0	150.8	397.6	396.1	356.9	263.4	
FEF ₈₅	148.5	135.1	119.7	-	243.4	226.0	210.3	-	
FEF ₉₀	103.3	-	-	39.6	170.1	-	-	86.7	
FEV _{0.5}	171.9	-	169.3	-	317.1	-	323.0	-	
FVC	191.0	196.6	195.0	352.2	391.4	456.4	418.7	657.8	
FEV _{0.5} /FVC	0.863	-	0.866	-	0.810	-	0.772		
<i>i</i> SVC	189.7				391.5				
SVC	188.1				383.6				
IC	167.2			245.7 ^c	354.3			471.0 ^c	
TLC ^d		311.6				613.0			
TLC	275.9				554.9				
<i>i</i> TLC	281.1				563.3				
<i>f</i> TLC	282.0				562.8				
FRC _{Pieth}		148.3				227.6			

Infant length		60 cm		75 cm				
Variables	Our Study	Castile et al., 2000	Jones et al., 2000	von Ungern-Sternberg et al., 2009	Our Study	Castile et al., 2000	Jones et al., 2000	von Ungern-Sternberg et al., 2009
FRC_{dyn}^e	110.9				200.3			
FRC_{st}^e	109.3				200.3			
RV^f		112.2				158.9		
$RV_{N_2}^e$	91.6				171.6			
ERV^g		33.3				63.2		
ERV^h	19.1				28.5			
FRC_{pleth}/TLC^d		0.473				0.366		
FRC_{dyn}/TLC	0.386				0.365			
FRC_{dyn}/TLC	0.386				0.361			
FRC_{dyn}/TLC	0.383				0.362			
$RV/TLC^{d,f}$		0.364				0.268		
RV_{N_2}/TLC	0.323				0.311			
RV_{N_2}/TLC	0.323				0.308			
RV_{N_2}/TLC	0.322				0.308			
RC_{50-75}^i	5.668		5.108		4.113		3.212	

^aVariables were generated with the prediction equations of the respective study. Forced expiration was generated by raised volume RTC from V30 except von Ungern-Sternberg et al. (2009) who used forced deflation from V40

^bNot reported

^cPassive expiration from V40

^d $TLC = FVC + (FRC_{pleth} - ERV)$

^eMeasured by MBNW

$$f_{RV} = FRC_{pleth} - ERV$$

g Difference between lung volume at end-forced expiration and the point at which a stable end-tidal expiratory level was re-established

$$h_{ERV} = FRC_{dyn} - RV_{N2}$$

i Rate constant for forced expiration computed as the ratio of the differences in flows and volumes between 50 and 75% of the FVC