Analysis of forced expiratory maneuvers from raised lung volumes in preterm infants

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Henschen, Matthias, Janet Stocks, Ah-Fong Hoo, and Paul Dixon. Analysis of forced expiratory maneuvers from raised lung volumes in preterm infants. J. Appl. Physiol. 85(5): 1989–1997, 1998.—During recent years it has been suggested that forced expiratory measurements, derived from a lung volume set by a standardized inflation pressure, are more reproducible than those attained during tidal breathing when the rapid thoracoabdominal compression technique is used in infants. The aim of this study was to evaluate the feasibility of obtaining measurements from raised lung volumes in unsedated preterm infants. Measurements were made in 18 infants (gestational age 26–35 wk, postnatal age 1–10 wk, test weight 1.4–3.5 kg). Several inflations [1.5–2.5 kPa (15–25 cmH2O)] were used to briefly inhibit respiratory effort before the rapid thoracoabdominal compression was performed. Conventional analysis of flows and volumes at fixed times and percentages of the forced expiration resulted in a relatively high variability in this population. However, by using the elastic equilibrium point (i.e., the passively determined lung volume, derived from passive expirations before the forced expiration) as a volume landmark, it was feasible to achieve reproducible results in unsedated preterm infants, despite their strong respiratory reflexes and rapid respiratory rates. Because this approach is independent of changes in expiratory time, expired volume, or applied pressures, it may facilitate investigation of the effects of growth, development, and disease on airway function in infants, particularly during the first weeks of life, when conventional analysis of forced expirations may be inappropriate.

airway function; rapid thoracoabdominal compression technique; raised-volume technique; respiratory function tests

FORCED EXPIRATORY MANEUVERS are routinely used to measure airway function in infants for clinical and research purposes (13). Although infants cannot be instructed to perform such maneuvers, they can be encouraged to breathe out as rapidly as possible through a face mask and pneumotachometer (PNT) by sudden application of a compressive pressure at end-tidal inspiration using an inflatable plastic cuff or jacket wrapped around the thorax and abdomen (13, 18, 19). Maximal flow at functional residual capacity (VmaxFRC), measured by this rapid thoracoabdominal compression (RTC), or squeeze, technique, is taken as an index of small airway function. Nevertheless, despite its value, this test has provided less information about respiratory problems in infants than similar tests in older children and adults (1). This is partly because tests in infants are limited to those that can be measured during normal tidal breathing, whereas standard tests in adults and children are made over the full vital capacity.

During the past few years, a new approach, known as the raised-volume RTC (RVRTC) technique, has been introduced. This technique assesses airway function over an extended volume range by delivering one (21) or a few (4, 10) large sighlike breaths to elevate lung volume before the RTC. Potentially, this enables full forced expiratory flow-volume curves, similar to those performed voluntarily by children and adults, to be obtained in infants. However, this technique has only been applied to sedated full-term infants beyond the neonatal period. The use of sedation is generally contraindicated for lung function tests in spontaneously breathing infants <4 wk postconceptional age (7).

This, together with the short epochs of natural, quiet sleep, frequent feeds, rapid and irregular breathing patterns, and strong respiratory reflexes, makes assessment of airway function notoriously difficult in preterm infants. There is, however, a real need for information about the growth and development of the respiratory system in late gestation and early postnatal life and the effects of disease and response to therapy during this period. Measurement of full forced expiratory flow-volume maneuvers could potentially provide such information. The aim of this study was therefore to evaluate the feasibility of using the raised lung volume technique to assess airway function in unsedated preterm infants.

MATERIALS AND METHODS

Subjects. Infants were recruited from the Neonatal Unit at the Homerton Hospital, Hackney, East London. Measurements were performed in 8 female and 10 male infants at 32–38 wk postconceptional age (postconceptional age = gestational age + postnatal age). Five of these infants had had no respiratory support, 10 had received assisted ventilation and/or supplementary oxygen for up to 5 days, and the remaining 3 were ventilated for >5 days and had received supplementary oxygen for >4 wk. Infant details are summarized in Table 1. All infants were studied unsedated, 0.5–1 h after a feed, during natural quiet sleep without additional
Table 1. Infant details

<table>
<thead>
<tr>
<th>Infant details</th>
<th>Male/female</th>
<th>Birth wt, g</th>
<th>Gestational age, wk</th>
<th>Postnatal age, days</th>
<th>Postconceptional age, wk</th>
<th>Test weight, g</th>
<th>Crown-heel length at test, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10/8</td>
<td>1,753±520</td>
<td>32.2±1.6</td>
<td>19 (5–71)</td>
<td>35.0±1.8</td>
<td>2,351±550</td>
<td>45.6±2.7</td>
</tr>
</tbody>
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Values are means ± SD, except for postnatal age, which is expressed as median and range.

Oxygen. Respiratory measurements were obtained with infants settled in the supine position, while heart rate, oxygen saturation, and end-tidal CO2 were monitored. The study was approved by the East London and City Research Ethics Committee. Informed written consent was obtained from the parents, who were usually present throughout the measurements.

Equipment and data acquisition. A transparent Rendell-Baker face mask (size 0, Ambu International, Bath, Avon, UK) was held over the infant’s mouth and nose, and a leak-free seal was created using therapeutic silicone putty (Carters, Bridgend, Mid Glamorgan, Wales). Flow was measured with a heated PNT (model 3500, Hans Rudolph, Kansas City, MO; dead space 6.8 ml, linearity 0–35 l/min) connected to a ±0.2-kPa (2-cmH2O) differential pressure transducer (Furness Controls, Bexhill, East Sussex, UK). Volume was obtained by digital integration of the flow signal.

Partial expiratory flow-volume curves were obtained as described in detail previously (17). Forced expiration was generated by inflating a jacket, which was wrapped snugly around the infant’s torso with the arms outside. The jacket extended from under the infant’s axillae to the iliac crest. The jacket consisted of a 17 × 16-cm polythene inflatable plate surrounded by a stiff outer fabric covering and was rapidly inflated from a 100-liter pressurized reservoir connected to the inflatable plate by a rigid large-bore (28-mm-ID) section of tubing. Pressure at the airway opening and jacket pressure were measured with ±5- and 10-kPa (50- and 100-cmH2O) differential pressure transducers, respectively (Furness Controls). Esophageal pressure (Pes) was recorded throughout the test in seven of the infants by using a microtip pressure transducer catheter (model 3FG, Draeger) (5). This catheter was inserted nasally into the distal third of the esophagus, and an occlusion test was performed to validate its accurate functioning (2). Flow and pressure signals were amplified and filtered above 10 Hz. Analog signals were digitized at 200 Hz (RASP, Physiologic, Newbury, Berks, UK) and stored on an IBM-compatible 486 personal computer.

Special features for the RVRTC technique. The equipment (Fig. 1) was adapted from that described by Feher et al. (4). The PNT was attached to a mainstream capnograph (CO2SMO, model 7100, Novametrics Medical Systems, Wallingford, CT) and connected to a Y piece (total resistance 0.570 kPa·l·s at a flow of 100 ml/s). The inspiratory side of the Y piece (3-way connector) received a constant airflow at 12 l/min via a pressure relief valve (Neopuff, model RD1000, Fisher and Paykel Healthcare, Auckland, New Zealand), which was set to 1.5-2.5 kPa (15–25 cmH2O).

Study protocol. The study commenced with measurements of \( V_{\text{maxFRC}} \) using the standard RTC maneuver (13, 17). Real-time signals of flow, volume, and pressure were displayed as time-based and x-y plots. Once 5-10 regular breaths had been recorded, the jacket was inflated at end inspiration to force expiration. Jacket pressure commenced at 2 kPa, then was increased at 0.5- to 1-kPa increments until flow at functional residual capacity (FRC) had reached a reproducible maximum (i.e., \( V_{\text{maxFRC}} \)) and higher pressures were causing a reduction of flow, indicating that apparent flow limitation had been achieved. At least three assessments of static jacket pressure transmission were performed at end-tidal inspiration (15).

The lowest jacket pressure required to achieve \( V_{\text{maxFRC}} \) during tidal maneuvers was then used during the raised-volume maneuvers. Measurements at raised lung volumes commenced with the pressure valve for the passive inflations set to 2 kPa (20 cmH2O). To ensure that no additional dead space was presented to the infant, manual inflations began immediately on connection of the capnograph and Y piece to the apparatus. Repeated occlusions of the expiratory side of the Y piece at a frequency approximating the infant’s respiratory rate resulted in passive inflations and deflations of the respiratory system (Fig. 2). Respiratory muscle relaxation was indicated by a change in Pes from negative deflections during active inspiration to positive inflections during passive inflations or from inspection of the flow-volume loops if no Pes trace was available. Once such relaxation had been achieved, the jacket was inflated at the end of a passive inflation to force expiration. Whenever possible, additional RVRTC maneuvers were also obtained at inflation pressures of 1.5 and 2.5 kPa (15 and 25 cmH2O).

Data analysis. The analysis software package was developed in collaboration with the Imperial College of Science, Technology, and Medicine. Criteria for acceptability of forced expiratory flow-volume curves were as follows: 1) jacket
inflation initiated within 100 ms of end inspiration, 2) peak expiratory flow achieved before 50% of previous tidal or passive inflation volume had been expired, 3) expiration proceeding beyond end expiratory level, and 4) regular tidal volume and end-expiratory level for the standard RTC or regular relaxed inflations for the RVRTC, as assessed by visual inspection of the time-based and flow-volume traces. Exclusion criteria included 1) leaks through face mask, PNT, or jacket and 2) significant glottic closure or flow transients. The mean of the three best flows at FRC from technically acceptable curves was calculated and reported as $V_{\text{maxFRC}}$.

Raised-volume data analysis. Initially all RVRTC data were analyzed in the conventional manner using only technically acceptable maneuvers that had a forced expired volume (FEV) within 10% of the highest value obtained (4). The following parameters were calculated: forced expiratory flows and volumes at 0.4, 0.75, and 1 s (FEF$_{0.4}$, FEV$_{0.75}$, and FEV$_{1}$, respectively) and forced expired flows at fixed percentages of the FEV (4) (e.g., MEF$_{50}$ and MEF$_{75}$, where MEF is the maximal expired flow when 50 or 25% of expired volume remains in the lung, i.e., equivalent to FEF$_{50}$ and FEF$_{75}$, respectively).

Inspection of preliminary data revealed that conventional analysis at fixed times or percentages of expired volume resulted in rather variable results in this population (Fig. 3A). This was largely due to subtle variations in the inflation volume and the expired volume, resulting in an inability to superimpose the FEF with any consistency. The following approach was therefore developed in an attempt to find a more reliable volume landmark with which to relate forced flows and volumes in this population.

The elastic equilibrium volume (EEV; i.e., the relaxed lung volume when elastic recoil of the chest wall and lung are equal and opposite) was calculated by extrapolating the expiratory time constant of the passive breaths preceding each forced expiration, with EEV being taken as the volume at which zero flow crossing occurred (Fig. 3B). The time constant was ensembled over the linear descending portion (usually the last 50–60% of expiration) of two to five passive expiratory flow-volume curves preceding the forced maneuver. To do this, the program applied least-squares regression to a specified segment ($\approx 45\%$) of the expiratory loop before.

**Fig. 2.** Time series recording of flow, volume, pressure at airway opening (Pao), jacket pressure (Pj), and esophageal pressure (Pes) before, during, and after a forced expiration from raised lung volume.

**Fig. 3.** A: alignment of 2 raised-volume forced expiratory maneuvers [thick line (a) and thin line (b)] at end of passive inflation to 2 kPa. Each forced maneuver is displayed with passive flow-volume curve recorded immediately before jacket inflation. Note poorly reproducible forced flows at all volumes above end-expiratory level. B: calculation of passive expiratory time constant ($t_{rs}$) by least-squares linear regression of descending linear portion of passive expiratory flow-volume curve of maneuver a in A. This time constant was extrapolated to zero flow to obtain elastic equilibrium volume (EEV). C: realignment of maneuvers a and b with respect to their EEV. In contrast to A, where curves were superimposed at end inflation to a set pressure, reproducible flows were obtained up to 6 ml/kg above EEV in this infant when curves were realigned according to their EEV. For clarity, only 2 maneuvers are shown, although this process could be performed with as many curves as desired. EEV + 2 and EEV + 4, flows at 2 and 4 ml/kg above EEV.
the RTC. Provided the coefficient of determination \( r^2 \) was \( \geq 0.98 \), the program then added the data from the same segment of the previous passive breath to the regression model and reassessed the correlation. This procedure was repeated for an increasing number of breaths before the forced maneuver until the correlation fell below the specified threshold. The process was repeated for each forced maneuver.

The program also provided the means to overlay the flow-volume loops from a number of separate RVRTC maneuvers by superimposing the individual pairs of curves (one passive breath with the ensemble time constant and its associated forced maneuver) and shifting them along the volume axis so that they were aligned at their calculated EEV (Fig. 3C). FEF could then be calculated at any number of user-specified points above or below the EEV. In the event of an acceptable forced expiratory maneuver but a poor-quality passive deflation immediately beforehand, which precluded accurate determination of the EEV for that trial, the program permitted manual realignment along the volume axis with respect to previously analyzed data. This option was utilized only if it resulted in clear superimposition of the descending portion of the forced expiratory curves.

To facilitate comparisons between infants of different weights and ages, we chose to standardize the volume above EEV at which flows should be calculated with respect to the infant's weight. This was believed to be justified, since there is a strong linear relationship between both tidal volume and compliance and body weight during infancy (14, 16). For clarity, only those values calculated at 2 and 4 ml/kg are reported here (Fig. 3C). These points were selected as examples to facilitate comparisons with \( V_{\text{maxFRC}} \), since it is recognized that young infants usually dynamically elevate their FRC by 2–4 ml/kg above their passively determined lung volume (11, 12).

Thus, after alignment of all the individual raised lung volume maneuvers, FEF at EEV \( (F_{\text{EEV}}) \) and at 2 and 4 ml/kg body weight above EEV \( (F_{\text{EEV} + 2} \) and \( F_{\text{EEV} + 4} \) were calculated (Fig. 3C). The aim was to superimpose at least three acceptable curves for each infant.

Reproducibility. In those infants in whom at least three technically acceptable measurements were available, the reproducibility of the different analytic approaches was compared by calculating the coefficient of variation \( (\text{coefficient of variation} = 100 \times \text{SD/mean}) \) based on three determinations for each parameter.

RESULTS

Forced expiratory maneuvers during tidal breathing and raised volumes were obtained in all 18 infants. Between three and nine (median 5) inflations were required to achieve respiratory muscle relaxation before the raised-volume maneuver. No adverse effects were observed. The augmentation of ventilation produced a temporary fall in end-tidal CO\(_2\) by 0.2–0.9 kPa from baseline levels. After the RVRTC maneuver the maximum time taken to resume spontaneous respiration was 15 s. Jacket pressure was 4.1 ± 1.1 (SD) kPa, with a mean jacket pressure transmission of 45% (range 33–55%).

Causes of failure. Of the 4–25 RVRTC maneuvers performed in each infant (median 14) only 40% were technically acceptable. Major reasons for failure were late glottic closure, flow transients, and early inspiration (Fig. 4), the latter often related to the difficulties in invoking respiratory muscle relaxation in this population. No technically acceptable data were obtained in two infants and another had fewer than three acceptable curves, thereby precluding reporting of results. Acceptance of only those curves with an FEV within 10% of the highest value resulted in exclusion of another two infants. Among the total population of 18 infants, only 5 continued to expire beyond 0.7 s and only one beyond 1 s, thereby precluding analysis of forced volumes and flows at these longer time intervals.

Reproducibility. Results from the remaining 13 infants who had three technically acceptable RVRTC curves with an FEV within 10% of the highest value are summarized in Table 2. For each infant the individual mean data, along with coefficients of variation, are shown only for those parameters where it was possible to obtain three technically satisfactory measurements. Thus no results are shown for \( F_{\text{EEV} + 2} \) in three infants in whom only two satisfactory tidal maneuvers could be obtained or for FEF and FEV at 0.4 s in the seven infants who did not consistently expire beyond 0.4 s. The variability of \( F_{\text{EEV} + 2} \) was generally lower than that
of other parameters with similar flows, e.g., $V_{\text{maxFRC}}$ and MEF$_{25}$.

Influence of changes in inflation pressure. Technically acceptable RVRTC data were obtained at different inflation pressures in 10 infants. As expected (21), forced flows and volumes at fixed times and percentages of the expired breath were dependent on the applied inflation pressures, higher values being achieved as pressures were increased (data not shown). By contrast, similar values of FEEV, FEEV$_{12}$, and FEEV$_{14}$ were obtained, irrespective of the applied pressures (Fig. 5).

Influence of timing of the raised-volume maneuvers. When the maneuvers were aligned along the volume axis according to the EEV, data previously deemed unacceptable due to methodological problems such as late jacket inflations, late release of inflation pressure, or early glottic closure were found to be readily superimposable (Fig. 6).

### DISCUSSION

In contrast to FEF measurements from raised volumes in older infants (4, 21), we experienced considerable technical and analytic problems and a high failure rate when applying this technique to a population of preterm infants during the first 3 mo of life. Consequently, when the infant remained asleep for long enough, it was necessary to perform a large number of maneuvers in an attempt to achieve three reproducible maneuvers within individual infants. However, by adapting the analytic technique so that the EEV, rather than the volume achieved from a preset pressure, was used as a volume landmark, we overcame many of these problems.

Methodological aspects. When the raised lung volume technique is applied to premature infants, several important methodological considerations must be taken into account.
into account. In contrast to measurements during tidal breathing, peak flows > 400 ml/s may be achieved during the RVRTC, even in infants with a history of chronic lung disease. This precludes the use of a PNT with a very low dead space, which would normally be selected for this population. The PNT employed in this study had a dead space of ~3 ml/kg to ensure an adequate linear range. This did not appear to have any adverse effects, and respiratory rates during spontaneous breathing were similar to those observed when a smaller device was used. Nevertheless, the application of techniques that can generate such high flows in such small subjects presents a challenge for manufacturers in the future.

In this study we were cautious not to expose the infants to excessive pressures in view of their immaturity and highly compliant airways and chest wall. During the initial pilot studies we attempted to use inflation pressures as low as 1.5 kPa but found that this rarely induced the desired relaxation (see below). Similarly, although we recognized the need to estimate the percentage of jacket pressure transmitted during the forcing maneuver, we preferred to perform this assessment at end-tidal inspiration, rather than after inflation to raised lung volume, to limit the pressures (elastic recoil pressure plus transmitted jacket pressure) to which the infant was exposed. Hayden and colleagues (10) showed that most outcome variables are pressure independent at a transmitted pressure between 2 and 2.5 kPa. For the raised-volume maneuvers, the use of the lowest jacket pressure required to achieve \( V_{\text{maxFRC}} \) during tidal maneuvers was selected in accordance with the protocol of the same group (21). The mean lowest jacket pressure required to achieve \( V_{\text{maxFRC}} \) in this study was 4.1 kPa, with a mean pressure transmission of 45%, such that the transmitted pressure to the intrathoracic structures was ~2 kPa at end-tidal inspiration. This should be sufficient to achieve flow limitation (10), especially in this population of preterm infants, many of whom had had respiratory problems at birth. The absolute driving pressures at higher lung volumes would have been even higher because of the increased recoil pressure of the lungs. Use of higher jacket pressures not only evokes excessive glottic closure in this population but can result in marked negative pressure dependency, which we were anxious to avoid.

Relative reproducibility. There are considerable difficulties in attempting to evaluate comparative reproducibility of different analytic techniques for forced expiratory maneuvers, since the calculated values will depend on prior exclusion criteria, the number of maneuvers analyzed, the absolute magnitude of the reported values, and indeed whether parameters are based on flow or volume. Because volume is the integral of flow, measures such as FEV, will always be less variable than those based on flow. Furthermore, any comparison of group mean data will be biased if there are missing data for different parameters in different subjects. In an attempt to address some of these issues, we based all calculations of reproducibility on three maneuvers, excluded those results where fewer data were available, and reported individual results for each infant (Table 2).

Estimation of EEV. In this study, EEV was estimated by extrapolating the linear descending portion of the passive expiratory flow-volume loop, i.e., the expiratory time constant. The accuracy of this approach was improved by calculating the ensemble time constant from several passive breaths before each forced maneuver. In addition to the achievement of complete muscle relaxation, a major assumption of this approach is that the respiratory system can be represented by a single time constant. We are confident that relaxation had been attained in the infants in whom data were accepted for analysis, although this was not necessarily achieved in every breath in every infant. Occasionally, despite having achieved relaxation, some intermittent spontaneous respiratory activity resumed. This was particularly marked if a longer expiratory pause was provided in the breath immediately before the jacket inflation, in an attempt to allow the infant to exhale more completely. This did not necessarily invalidate the forced expiratory maneuver but did necessitate calculating the passive time constant from an earlier breath in the sequence. We have subsequently revised our protocol so that attempts to achieve complete passive expiration are recorded during trials separate from those in which forced expiratory maneuvers are performed.

The assumption of a single time constant is more complex, particularly if this approach is to be used to assess airway function in infants with elevated airway resistance. In such infants a rise in resistance toward end expiration could lengthen the time constant over the latter portion of the expiratory flow-volume curve, causing overestimation of the volume intercept and, hence, errors in the calculated EEV (3, 6). Although it was not possible to obtain a linear relaxed curve from every infant during every maneuver, extrapolation of passive flow-volume curves from raised volumes proved far less problematic in this study than when a similar approach was attempted after end-inspiratory occlusions during tidal breathing (i.e., the single-breath technique) (6). Results were accepted only if a time constant with \( r^2 \geq 0.98 \) could be calculated over \( \geq 45\% \) of the expired volume toward end expiration (a portion that represented well over 75% of the duration of expiration in most of these infants). We found that extrapolation of this portion of the curve coincided with complete expiration to passive resting lung volume in those infants in whom this could be achieved (Fig. 7). The curvilinear appearance of the initial portion of the passive curves was usually attributable to flow transients that occur during early expiration on release of an airway occlusion as a result of gas decompression through the PNT (Figs. 7 and 8), the magnitude of which is dependent, at least partially, on the speed at which the occlusion is released. This portion of the curve was always excluded when the time constant was estimated.

Ideally, the infants would have been allowed to expire fully to their passively determined lung volume after
lung inflation to ensure an accurate estimate of EEV. This may be relatively easy to achieve in older infants, but when young and preterm infants are studied, a relatively rapid ventilatory rate may be necessary during lung inflations to overcome the strong respiratory drive. This inevitably introduced a small degree of positive end-expiratory pressure. Although this would not have influenced results had we used only conventional methods of analysis, it did necessitate extrapolation of the flow-volume curves to zero flow if we were to estimate EEV in this study. However, whenever possible, we compared the EEV estimated by extrapolation of the time constant with that achieved when the infant had expired fully to the passively determined lung volume and found close agreement (Fig. 7).

A further potential problem in using the EEV as a volume landmark is that respiratory mechanics, and hence time constant, could change during the period of testing as a result of the lung inflations. In the present study we did notice a change in time constant from one inflation to another in a few of the infants. However, when this occurred, it appeared to be associated with a change in the end-expiratory or the inspired volume, with extrapolation of the flow-volume curves to zero flow still resulting in a consistent EEV (Fig. 8).

Despite these potential problems, the use of the EEV as a volume landmark with which to align the forced expiration resulted in remarkably consistent overlay of the data and, hence, calculated parameters, in contrast to results initially obtained when the conventional analytic approach was used. Advantages of the “EEV” approach include the fact that there are fewer exclusions due to technically inadequate data and that it is not dependent on achieving maneuvers with an FEV within 10% of each other. This means that the data collection period can be shortened, which will increase the success rate of the technique, particularly when applied to young, unsedated infants.

In contrast to previously reported studies (4, 21), equipment automated with respect to timing of the lung or jacket inflations was not available in our laboratory. The use of such equipment might have reduced the variability in forced flows at fixed times and percentages of the expired breath and would have probably increased the volume range over which we were able to superimpose the forced expiratory curves. Nevertheless, the analytic approach based on EEV enabled reproducible results to be obtained, despite the lack of optimal equipment, and had the advantage of allowing us to customize the pattern of ventilation to individual infant requirements. Furthermore, the use of automated equipment would not have overcome the problems associated with glottic closure and short expiratory duration encountered in this population. Variability of breathing patterns, strong reflexes, rapid respiratory rates (up to 75 breaths/min), and short expiratory times present a real challenge when the raised-volume technique is applied to preterm or newborn infants and may preclude the use of a fully automated system.

The duration of forced expiration was <0.5 s in most of these infants, with relatively few of them consistently expiring beyond 0.4 s. It was thus impossible to calculate any timed forced volumes or flows routinely at the conventional time intervals used in older subjects. Because there is no information on how forced flows or volumes at intervals of <1 s relate to measures of FEF₁ or FEV₁, such measures are unreliable parameters on which to base studies of the effect of growth and development or disease on airway function in the very young.

Similar problems are experienced when trying to decide on the optimal pressure with which to inflate the infant’s lungs. There is no consensus on this matter, with some centers using a fixed pressure of 3 kPa (30 cmH₂O) (4), whereas others apply a range of pressures.
between 1.5 and 3 kPa (21). Other authors, using passive deflation techniques, have suggested that 4 kPa (40 cmH2O) is required to attain total lung capacity in infants (9, 13), yet few operators would be willing to impose such high inflation pressures during application of the raised-volume technique. We were reluctant to use pressures as high as 3 kPa in preterm infants and initially based all our measurements on inflation pressures of 2 kPa. Subsequently, we investigated the effects of applying a range of pressures but found that at 1.5 kPa (15 cmH2O) it was often difficult to override respiratory drive and induce respiratory muscle relaxation, whereas the use of 2.5 kPa more frequently induced glottic closure and invalidated the results. Having determined that the EEV approach is independent of applied pressures (Fig. 5), we would probably recommend the use of 2 kPa (20 cmH2O) as a standard in preterm infants, although higher pressures may be necessary and advisable in older infants.

Agreement has still to be reached regarding optimal inflation pressures when the raised-volume technique is used. Infants occasionally take a deep sigh at the end of passive inflations (i.e., Head's paradoxical reflex) (20), thereby almost doubling the inspired volume above that achieved at an inflation pressure of 2–2.5 kPa (Fig. 8). We have seen this response intermittently even in older infants and have noticed its occurrence during other lung function tests, for example, during the sighs that sometimes occur after release of airway occlusions during assessments of passive mechanics or plethysmographic lung volumes. It is well known that the distribution of ventilation differs between spontaneous and paralyzed breaths (22). It may well be that the pattern of recruitment of the respiratory musculature during spontaneous efforts is far more efficient at inflating the lungs than that resulting from imposition of positive pressure at the airway opening. In addition, the application of positive airway pressures may evoke reflex changes in chest wall compliance or airway mechanics, thereby limiting the degree of inflation that is achieved.

Until some international agreement is reached with respect to the optimal inflation pressure to apply, the use of an alternative volume landmark such as that offered by the EEV, in addition to conventional analysis, would offer the possibility of comparing results not only within laboratories but between them. This could facilitate the search for the optimal protocol and the establishment of reference data. However, flows at volumes above EEV are likely to be more informative in separating the effects of growth and disease than those at EEV itself. The latter will always fall below FRC, at a point when flows will tend to be low in all infants. In this study we have reported values for FEEV and FEEV + 4. Since we knew that such flows should approximate the VmaxFRC obtained during tidal RTC maneuvers in each infant, thereby facilitating comparisons of relative reproducibility. In addition, it was always possible to superimpose the forced expiratory curves at these points. Values for FEEV + 4, which were similar to MEF25 in the majority of infants, were routinely available in all infants. However, further work is required to ascertain which indexes prove to have the greatest sensitivity and specificity in detecting airway disease or response to therapy in this age group. In several of the infants, reproducible forced flows could also be obtained at much higher lung volumes (e.g., up to FEEV + 9 in Fig. 5). However, in the absence of automatic equipment to improve timing of jacket inflations and release of airway occlusions and in the presence of frequent glottic closure in response to the jacket inflation, it was not possible to routinely achieve reproducible flows at high lung volumes in these infants.

In this study we followed the approach of Feher et al. (4) and analyzed only curves that were within 10% of the highest value obtained. Not only did this increase the failure rate of the technique, but we still observed considerable variability with respect to forced flows and volumes at fixed times or percentages of the expired breath. This was primarily due to the fact that although we selected breaths in which overall volume change was similar, there were subtle differences in the volume delivered at any given pressure and the volume expired. Variations in inflation volume occur when preset pressures are used, if there is any variability in the duration of inflations or respiratory mechanics, whereas variations in expired volume result from differences in inflation volume and duration of expiration, with young infants frequently making inspiratory efforts before residual volume has been achieved. Circumstances can thus arise whereby a slightly smaller inflation volume coupled with a longer duration of expiration may give a FEV similar to that achieved with a larger inflation volume but earlier inspiration. Under these circumstances, the flows obtained at fixed times or percentages of the FEV will vary, as found in the current study (Fig. 3A). Achieving consistency of applied pressures or volumes can also be a problem in older infants, with some centers applying regression analysis to a range of pressures to calculate results (21).

In conclusion, although further refinements are required, particularly with respect to estimating the EEV more objectively, the use of EEV as a volume landmark appears to be a promising approach when the raised-volume technique is applied to young or sick infants in whom sedation may be inappropriate (8) but in whom a knowledge of airway growth and development is very important. Furthermore, this may not only facilitate the achievement of more reliable results in this age group but provide a means to compare data within and between centers until a more standardized approach to data collection and analysis has been developed. However, further refinements are required, particularly with respect to suitable automation for use in such rapidly breathing subjects. In addition, the observation of marked increases in volume during spontaneous sighs above that achieved by 2.5 kPa of inflation pressure is of considerable interest. This phenomenon needs systematic investigation in the future, inasmuch as it suggests that the determination of total lung
capacity may differ between adults and preterm infants.

The authors thank Sarah Reid for assistance during this study and Novametrix for supplying the mainstream capnograph.

This study was supported by SIMS Portex, the Foundation for the Study of Infant Deaths, and the Dunhill Medical Trust. M. Henschen was supported by the Deutsche Forschungsgemeinschaft.

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Received 8 December 1997; accepted in final form 27 July 1998.

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