Lung volumes and lung mechanics in anesthetized children

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To my late mother

CONTENTS

1. ORIGINAL STUDIES

This thesis is based on the following papers, which are referred to in the text by their Roman numerals (I-IV).

I. Thorsteinsson A, Jonmarker C, Larsson A, Vilstrup C, Werner O.
Functional residual capacity in anesthetized children: Normal values and values in children with cardiac anomalies.
Anesthesiology 1990; 73: 876-881.

II. Thorsteinsson A, Larsson A, Jonmarker C, Werner O.
Pressure-volume relations of the respiratory system in healthy children.
Am J Respir Crit Care Med 1994; 150: 421-430.

III. Ingimarsson J, Thorsteinsson A, Larsson A, Werner O.
Lung and chest wall mechanics in anesthetized children. Influence of body position.
Am J Respir Crit Care Med 2000; 162: 412 -417.

IV. Thorsteinsson A, Jonmarker C, Werner O, Larsson A
Airway closure in anesthetized infants and children. Influence of inspiratory pressure and volumes.
In manuscript.

Papers I-III in the Appendix are reprinted with kind permission of the respective journals/publisher. This is gratefully acknowledged.

2. ABBREVIATIONS

ASA status	American Society of Anesthesiologists physical status scale
ATPS	Ambient temperature and pressure of water vapour saturated gas
BTPS	Body temperature and pressure of water vapour saturated gas
C_{lung}	Lung compliance
C_{rs}	Compliance of the total respiratory system
CC_{20} (CC_{30})	Closing capacity measured by 20 or 30 cmH_2O airway pressure
CHD	Congenital heart diseases
CP	Closing point
E_{cw}	Chest wall elastance
EEV	Elastic equilibrium volume, equivalent to FRC in awake subjects
ERV	Expiratory reserve volume (obtained as the volume between 0 and ?20 cmH_2O on the P-V curve)
FRC	Functional residual capacity
F_{IO_2}	Fraction of inspired oxygen
IC	Inspiratory capacity
MBAME	Multiple breath alveolar mixing efficiency
P_{aw}	Airway pressure
P_e	Esophageal pressure
PEEP	Positive end-expiratory pressure
P-V	Pressure-volume
RV	Residual volume
SF_6	Sulfur hexafluoride
TLC	Total lung capacity
VC_{20} (VC_{30})	Vital capacity, the volume between RV and peak inspiratory pressure of 20 (30) cmH_2O
ZEEP	Zero end-expiratory pressure

3. Abstract

The thesis was intended to fill gaps in the knowledge regarding the normal development of lung volumes and lung mechanics in children, from young infancy to the mid-teens. In particular, data were previously lacking regarding pre-school children. The studies were done during anesthesia and muscle relaxation.

Measurements

? Absolute lung volume was obtained with a tracer gas method (sulfur hexafluoride washout).
? Relation between airway pressure and lung volume (pressure-volume relation of the respiratory system) was asssessed during a slow intermittently interrupted expiration from 30 to 0 cm H_2O of airway pressure.
? In a further study, attempts were made to separate P-V relations of the respiratory system into lung and chest wall components. This was done by analyzing esophageal pressure - that was taken to represent pleural pressure - in addition to airway pressure.
? In a final study, a tracer gas was again used, now in an attempt to find the point during expiration, where significant airway closure occurred.

Main findings

I. Absolute lung volumes, per kg body weight, were less in young infants than in older children.
II. The most marked qualitative change (size factor eliminated) in the pressure-volume relation of the respiratory system occurred during infancy.
III. In the supine position, esophageal pressure paradoxically remained positive as expiration continued towards low lung volumes and even increased in some instances. When an attempt was made, anyway, to separately assess the various contributions to ”total elastance”, the chest wall contribution was relatively minor (about $1/10^{th}$ in infants).
IV. The airway ”closing phenomenon” occurred at a higher lung volume when the measurement maneuvre included a deep foregoing inspiration (to 30 rather than 20 cm H_2O of airway pressure).

Interpretation and possible clinical implications of findings

I. The lung is smaller, in relation to weight, in infants than in older subjects. Yet it is known from other studies that the rate of oxygen consumption at rest is greater. This suggests that infants will have reduced tolerance to stresses such as increased oxygen requirement (e.g. due to fever), apnea (e.g. during tracheal intubation), and restriction of lung capacity (e.g. resection of lung parenchyma, pneumonia, hydrothorax).

II. The respiratory system of small infants has less elastic recoil than that of older subjects. This probably reflects a low elastin content in the lungs, as described by others.

III. In the clinical assessment of mechanically ventilated infants, it is seldom worth the effort to separate P-V relations into lung and chest wall components - the simpler alternative of studying only respiratory system P-V relations will give an adequate picture of lung mechanics, if the infant is deeply sedated and temporarily relaxed. The same is probably true also for older children.

IV. High insufflation pressures will recruit otherwise collapsed airways, that will close early during the subsequent expiration. The relevance of this finding to conditions prevailing during regular breathing (mechanical or spontaneous) is, at most, speculative.

4. Introduction and background

Studies of lung mechanics that are easy to perform in well-informed, co-operating adults are often difficult to do in awake infants and children. Concerning lung mechanics there is, therefore, a gap in our knowledge as regards the youngest age groups. Deductions based on older children and teenagers do not give sufficient clues since, e.g., *post mortem* studies show that major anatomical and histological changes take place in the lungs and surrounding structures during the first eight years of life. In this thesis, the practical problems of performing pulmonary function tests in preschool children were circumvented by doing them during general anesthesia.

4.1. Changes in the lung

Dunnill (1) compared lungs from ten deceased children (newborn to 8 years old) with adult lungs. He found that the number of alveoli and respiratory airways increased more than tenfold between birth and adult life (Fig. 1A). This increase seemed to occur mainly during the first eight years. Thereafter, the increase in lung volume took place by an increase in the linear dimensions of the existing alveoli (Fig. 1B). The mean number of generations of airways increased from 21 to 23, from three months to eight years of age. This increase occurred in the most distal respiratory airways. There was a linear relationship between the surface area of the air-tissue interface and the body surface area during the period of growth (Fig. 1C).

Keeley *et al.* (2) found that the content of elastin in human lung parenchymal tissue was 6% during fetal development, rising to 12% over the first year of postnatal life, and remaining at this level until at least 28 years of age (Fig. 2).

Fagan (3) studied the pressure - volume (P-V) relationship of the lungs and found in younger children that P-V curves normalized to total lung capacity increased steeply from the elastic equilibrium volume (EEV) and leveled off at lower pressures (Fig. 3).

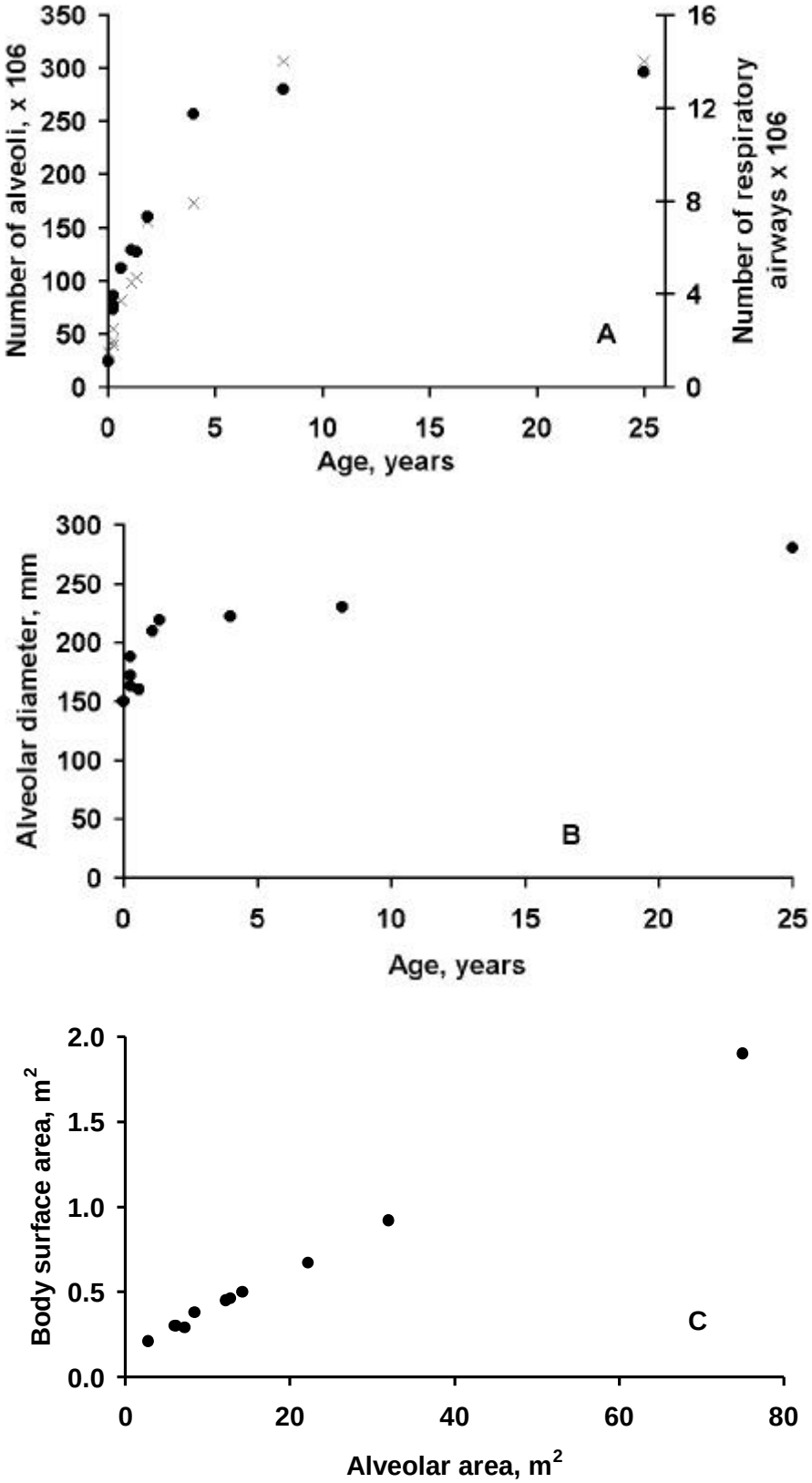

*Figure 1. Data from Dunnill (1). (*A*) The increase in the number of alveoli (?) and respiratory airways (?) during growth. (*B*) The increase in alveolar diameter during growth. (*C*) The relation of alveolar area and body surface area.*

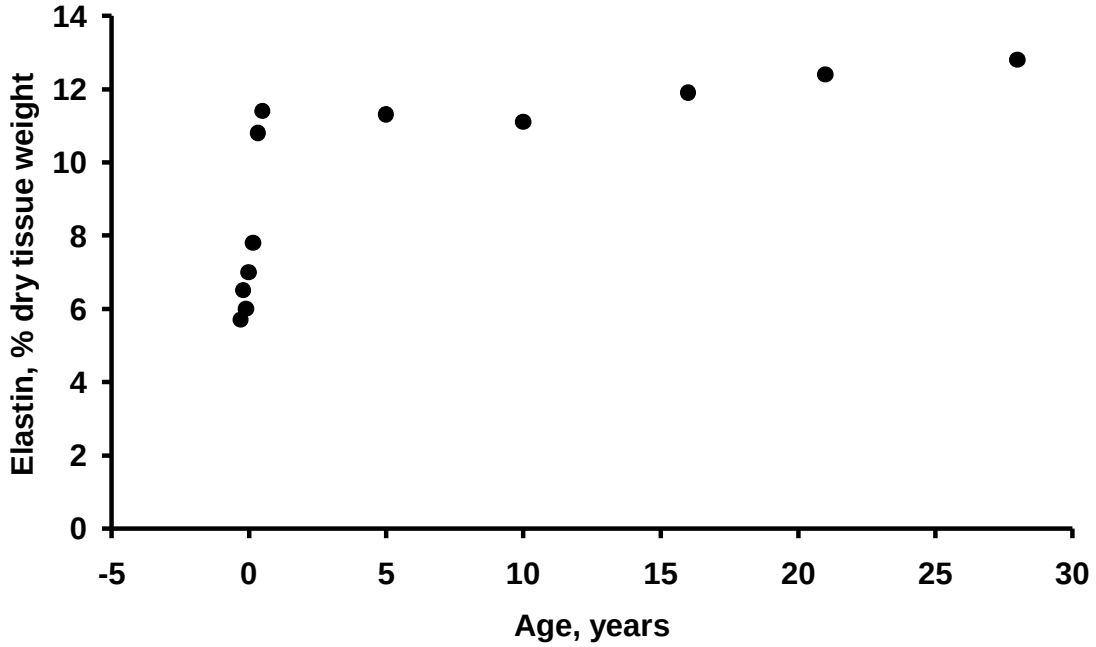

Figure 2. Data from Keeley (2). The increase in elastin content of the lung during growth.

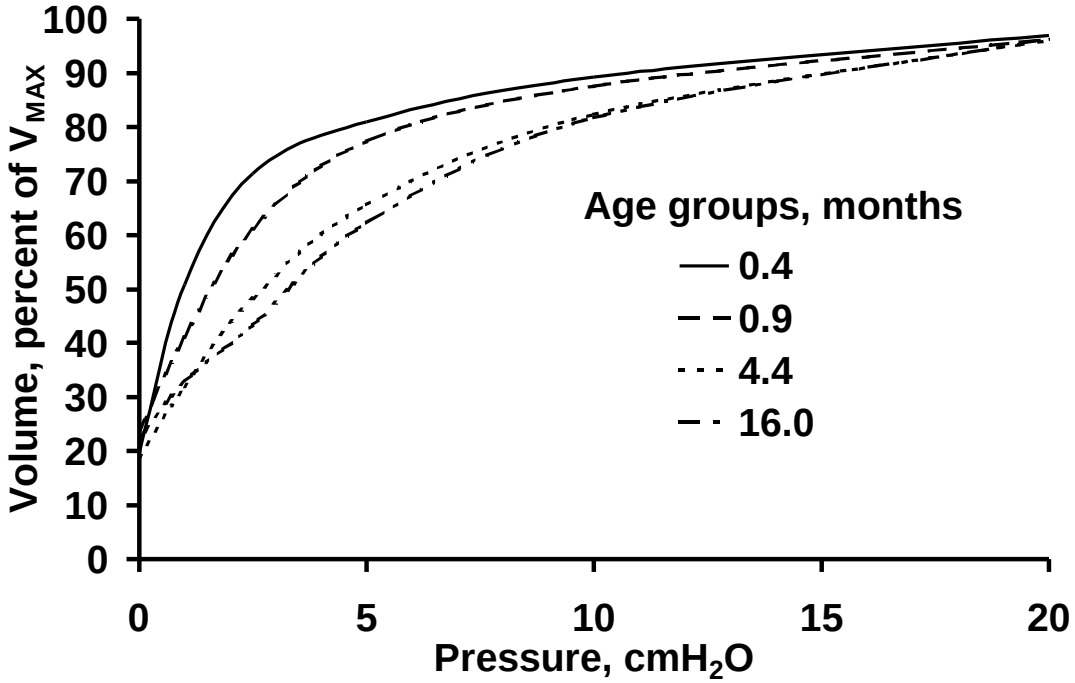

Figure 3. Pressure - volume relationship of lungs. Data from Fagan (3).

4.2. Changes in the thoracic wall

Like the lungs, the thoracic wall changes with age (4). At birth the ribs extend horizontally from the vertebral column, and the cross section of the thorax is more circular than in adults. In contrast to the adult, the newborn cannot increase the volume of the rib cage by raising the ribs, which enlarge the volume by both the “bucket handle” and a “pump handle” effect. With increasing age there is a progressive mineralization of the ribs and an increase in the ratio of bone to cartilage. Dorsal inclination of the ribs at their vertebral ends is also more marked, bringing the thoracic cavity alongside and dorsal to the spine. In front view the thorax assumes the shape of a Gothic arch in older children compared with a Roman arch in the infants. An important part of the changes in chest wall compliance during growth is due to the increased gravitational effect with age on the abdominal-diaphragmatic component of the chest wall. In addition, the increase in the bulk of the respiratory muscle with growth may play a part in the stiffening of the chest wall.

5. AIM OF THE STUDY

The general purpose of the thesis was to clarify age-related changes in lung function in infants and children during general anesthesia and muscle relaxation. To effect this methods for respiratory measurement that are, usually reserved for use in specialized laboratories were adapted for bedside use in the operating room or in the ICU.

Specific aims were to:

- Measure EEV using SF_6 (sulfur hexafluoride) as tracer gas.
- Compare EEV in healthy children and children with cardiac anomalies.
- Study P-V relation of the respiratory system and to divide the findings into lung and chest wall components.
- Investigate possible anomalies in the relation between esophageal pressure and lung volume, due to body position (notably the supine position).
- Measure closing capacity (CC) using a SF_6 as tracer gas.
- Study the occurrence of airway closure during tidal breathing using two different inspiratory pressures during the measurement maneuver.

6. PATIENTS AND SUBJECTS

Paper I.

Seventy-four children, 30 girls and 44 boys, 0.1 – 11.2 years of age, candidates for lower abdominal or urological procedures, all without sign of cardiac or respiratory disease.

Twenty-one children, 9 girls and 12 boys, 0.2 – 6.9 years of age, having congenital heart malformation. Results obtained in 12 of the children were published previously (5).

Paper II

Forty-eight children, 20 girls and 28 boys, 0.1 – 15.7 years of age, scheduled for lower abdominal or urogenital surgery. None had a history of lung disease or asthma, and physical examination indicated normal lung and heart function. EEV measurements from 43 of the children were included in Paper I.

Paper III

Seventeen children, 2 girls and 15 boys, 0.2 – 15.5 years of age, scheduled for urogenital or lower abdominal surgery. None had history of lung disease and physical examination indicated normal lung and heart function.

Paper IV

Eleven children, 7 girls and 4 boys, 0.6 – 12.8 years of age, scheduled for elective surgical procedures requiring general anesthesia and intubation. The children had no signs of respiratory disease.

Table 1. Demographic data

	Number	**f/m**	**Age, years**	**Weight, kg**	**Height, cm**
Paper I					
Normal	*74*	*30/44*	*2.6 (0.1-11.2)*	*14 (3.8-36)*	*92 (52–146)*
*CHD**	*21*	*9/12*	*1.5 (0.2-6.9)*	*8.7 (5.1-22.2)*	*74 (56–127)*
Paper II	48	20/28	3.3 (0.1-15.7)	17.5 (2.4-54)	105 (47-170)
Paper III	17	2/15	2.3 (0.2-15.5)	13.2 (5.2-56)	92 (59-172)
Paper IV	11	7/4	3.4 (0.6-12.8)	15.5 (7.6-46)	94.5 (66-155)

*CHD = congenital heart diseases. Values are median and range in parentheses.

Except for the children in Paper I with congenital heart disease, all of the children had ASA status I or II.

In all of the studies, informed consent was obtained from the parents and from the child, if old enough. The local Human Studies Committee also approved the studies.

7. METHODS

7.1. ANESTHESIA AND VENTILATION

In most cases (71%) anesthesia was induced with intravenous thiopental. Inhalation induction was used in 21% of cases and other methods in 8%. The children were given a muscle relaxant and tracheally intubated with cuffed tubes. Anesthesia was maintained with halothane in oxygen/nitrogen (F_{IO_2}=0.6). Ventilation was controlled, and an end-tidal P_{CO_2} of 4 to 5 kPa was aimed at.

7.2. MEASUREMENTS

Two types of measuring equipment were used.

- Equipment for EEV measurement, including an SF_6 analyzer.
- Apparatus for measuring P – V relationship.

7.2.1. MEASUREMENT USING SULFUR HEXAFLUORIDE AS A TRACER GAS

Sulfur hexafluoride was used in low concentration. The low alveolar concentrations increase the margin of safety, as a very little alteration in the supply of other gases was needed. There was no interference from clinically relevant gases such as CO_2, N_2O or the inhalational agent used: halothane (6).

7.2.1.1. MEASUREMENT OF EEV (PAPERS I AND II)

EEV was measured with a multiple-breath washout technique using SF_6 as a tracer gas (fig. 4).

The method has previously been described in detail (7-9): Briefly, the tracer gas concentration was measured in the apparatus deadspace between the endotracheal tube and the Y-piece with an infrared transducer placed over a cuvette with windows. SF_6 was washed in through a dispensing device, which mixed SF_6 in proportion to the instantaneous inspiratory flow. In that way, a uniform inspired concentration was achieved even with non-constant inspiratory flow. Wash-in continued until a stable end-tidal concentration of approximately 0.5% was attained. SF_6 washout was started by stopping tracer gas delivery between two inspirations, and was considered complete when the mean expired concentration was less than 0.001%. Signals representing flow and SF_6 concentration were fed into a computer which displayed inspired and expired tidal volumes and the tracer gas concentration in each breath, and calculated EEV when washout was completed.

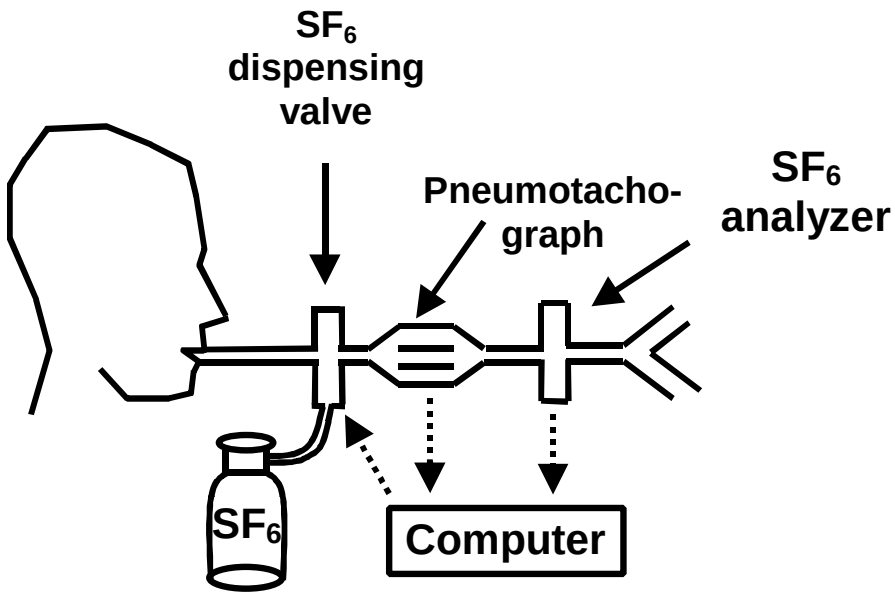

Figure 4. The setup of the EEV measurement system. The dashed arrows represent flow of information

EEV was calculated as the volume of SF_6 washed out divided by the alveolar concentration at the end of the wash-in period. The value was converted to BTPS condition, and apparatus deadspace subtracted. Apparatus deadspace varied from 8 ml in the youngest to 38 ml in the oldest, depending on the size of the pneumotachograph and on whether a heat-moisture exchanger was used or not. Tidal volume, mean expired SF_6 concentration, end-tidal SF_6 concentration, and the SF_6 volume obtained in each expiration were stored for later analysis of the washout curve.
Airway flow was measured with a heated Fleisch pneumotachograph size 00, 0 or 1 connected to a Validyne MP 45 differential pressure transducer (or standard flowmeter of Servoventilator for children with CHD in Paper I). Tidal volume was obtained by integration of the flow signal. EEV was measured approximately 15 min after induction of anesthesia in normal children (30 – 45 min after induction in children with CHD, Paper I) The measurement was performed prior to surgery and with the patient in supine position. To control the volume history of the lungs and counteract atelectasis formation that regularly appears during anesthesia in the dependant part of the lung (10, 11), a few deep breaths were given before wash-in in children whose lungs were manually ventilated. In most children whose lungs were mechanically ventilated, the lungs were expanded with 5 cmH_2O of positive end-expiratory pressure (PEEP) until 0.5 – 2 min before washout, when the ventilator setting was switched to zero end-expiratory pressure (ZEEP). To ascertain that ZEEP was present during the measurement of EEV, the last expiration before tracer gas washout was prolonged.

7.2.1.2. MEASUREMENT OF CLOSING CAPACITY (PAPER IV)

The set-up is shown in Paper IV. The flow and SF_6 signals were obtained as in the EEV measurement but the child was disconnected from the ventilator and connected to a 3-liter syringe containing equal parts of oxygen and air (F_{IO_2}=0.6). The measurements were made as follows: From EEV the lungs were deflated to a pressure of –20 cmH_2O, as assessed by a water manometer, a level considered to reflect residual volume (RV). A bolus of 100% SF_6 (0.5 ml/100 ml EEV) was injected into the airway close to the tracheal tube and the lungs were inflated to +20 cmH_2O or +30 cmH_2O. During the subsequent deflation to –20 cmH_2O, which was done slowly over 7-9 s to avoid dynamic compression of airways, signals representing expired tracer gas concentration and expired volume were processed by the computer and subsequently plotted on a diagram depicting volume vs. concentration.

The expiratory curves were placed in random order and analyzed by two independent observers. The closing point (CP) was taken to be the point at which upward departure occurred from a "best –fit" line through the latter half of phase III (12, 13). The volume from the beginning of the exhalation to closing point was noted. Corrections were made for serial deadspace in the airway and apparatus and for the volume of the SF_6 bolus. The serial deadspace volume was obtained from the first washout breaths during EEV measurements as the volume expired when the SF_6 concentration had reached 50% of the tracer gas concentration at end of phase III (9). When calculating CC, the deadspace value was corrected for the difference in apparatus deadspace during EEV- and closing-measurements. To find CC, the following calculation was made. First, Expiratory reserve volume (ERV) was found as the volume between EEV and RV. The vital capacity (VC) from RV to + 20 (or 30) cmH_2O (VC_{20} and VC_{30}) was recorded. The volume above EEV, i.e., inspiratory capacity (IC) was found as VC_{20} (or VC_{30}) minus ERV.

EEV on the expiratory curve was assumed to occur during expiration when a volume corresponding to IC had been exhaled. CC was therefore found as IC_{20} (or IC_{30}) + EEV ? the volume above CP.

7.2.1.3. INDEX OF VENTILATION INHOMOGENEITY (PAPER IV)

Multiple breath alveolar mixing efficiency (MBAME) was defined as 100 x TO_{ideal}/TO_{actual}, where TO_{ideal} is the ideal number of turnovers (cumulative expired volume/EEV) needed to wash 90% of EEV free of tracer gas, and TO_{actual} is the actual number of volume turnovers (14). In the calculations of MBAME, volume turnovers were corrected for deadspace.

7.2.2. MEASUREMENT OF MECHANICS OF THE RESPIRATORY SYSTEM (PAPERS II AND III)

The P-V relationship of the total respiratory system was studied in Papers II and III. The pressure was measured at the airway opening during a condition of zero airway flow and was therefore taken to represent alveolar pressure. In Paper III the esophageal pressure was also recorded, in order to obtain an estimate of pleural pressure.

7.2.2.1. MEASUREMENT OF THE AIRWAY PRESSURE

The set-up (Fig. 5) included a pressure transducer, a heated Fleisch pneumotachograph connected to a differential pressure transducer, an ink jet recorder, a computer, an X-Y recorder, a flow interrupter, a supersyringe, and a water manometer. The flow interrupter consisted of an electromagnetic valve placed over a soft rubber connector (closing time 30 ms). Data were analyzed by computer, and the processed curves written on paper.

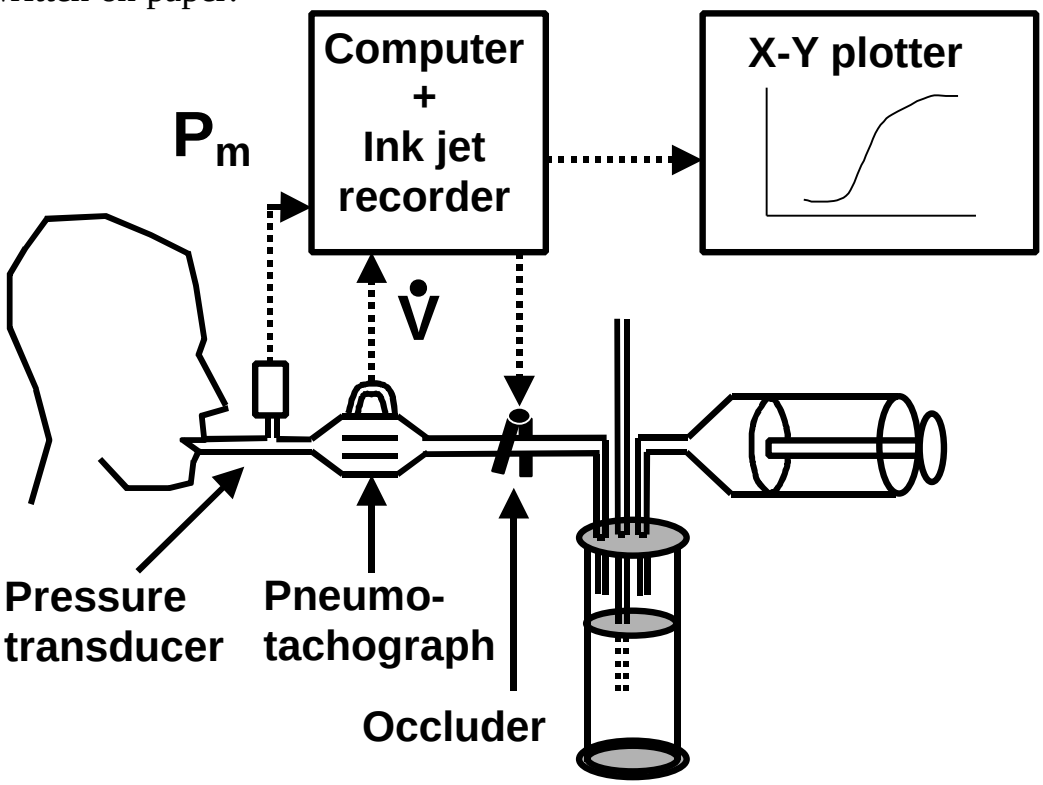

Figure 5. The setup of the pressure - volume measurement system. The dashed arrows represent flow of information

The measurement sequence was as follows: After the lungs had been expanded by 5 - 6 manual bag insufflations, (F_{IO_2}=0.6), they were inflated with the syringe (also containing 60% O_2) to a pressure of 25 - 30 cmH_2O in children less than one year of age and to 35 - 40 cmH_2O in older children. The lungs were kept inflated for 2 - 3 s, and the computer was

activated. This resulted in closure of the interrupter for 1 s after which the lungs were deflated over 15 - 25 s by retracting the plunger of the syringe. Deflation continued until airway pressure had reached a preset lower limit of -10 to -20 cmH_2O, when the computer stopped the measurement sequence. During deflation the flow interrupter closed for 0.16 s every 0.32 s. In order to avoid noise caused by the interrupter itself, to allow it time to close (0.03 s) and to obtain an acceptable pressure plateau, only the pressure signal between 0.08 and 0.12 s after the start of closing the interrupter was processed. The mean airway pressure value during this period was taken to represent the alveolar pressure during the occlusion. To obtain the lung volume decrement during interrupter opening, the flow signal was integrated over one interrupter cycle, i.e., 0.32 s. Flow and pressure signals were A/D-converted every 10 ms for processing by the computer. The series of volume decrements and corresponding pressures was used to construct the P-V curve.

7.2.2.2. MEASUREMENT OF THE ESOPHAGEAL PRESSURE

Esophageal pressure was measured as follows (Fig. 6). One of two sizes of latex balloon catheters, depending on the age of the child, was used for esophageal pressure registration; the balloon was 50 or 100 mm long with a diameter of 18 or 36 mm, respectively (when inflated to 5 cmH_2O of pressure). After endotracheal intubation and while the child was supine and breathing spontaneously, i.e. before the non-depolarizing muscle-relaxant was given, the catheter was passed via the mouth and esophagus into the stomach. The balloon was insufflated with 2 (5) ml air and thereafter exsufflated to a pressure of minus 5 cm H_2O. 0.3 (0.8) ml of air was then introduced via a three-way tap to bring the balloon within its working range and the catheter was connected to a pressure transducer. The pressure in the balloon was registered on an ink jet recorder.
The position of the balloon in the stomach was confirmed by recording a positive pressure during inspiration. The catheter was then slowly withdrawn into the esophagus until the pressure became negative during inspiration and a further approximately 3 cm to clear the balloon of the cardiac sphincter. Correct positioning was confirmed by airway occlusion at end-expiration during spontaneous breathing. If the ratio between the esophageal and the airway pressure change was in the range 0.94 - 1.00, the position was considered satisfactory; otherwise, the position or volume of the balloon was adjusted (15).

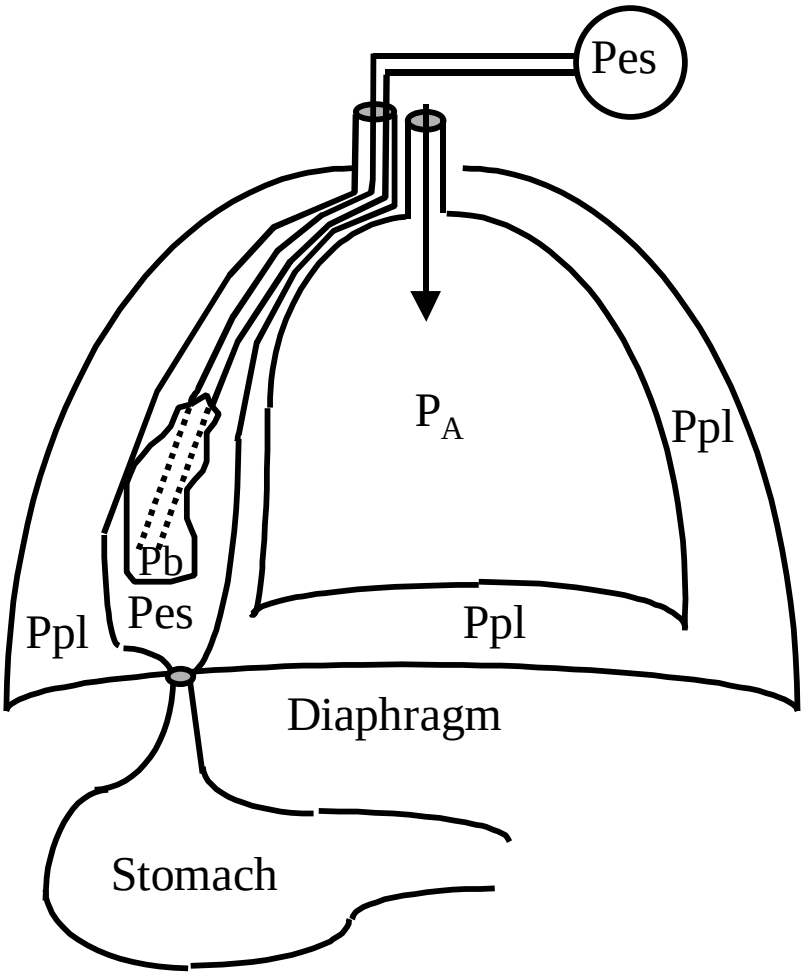

Figure 6. The esophagus pressure reflects the pressure of the pleura. P_{pl} = pleura pressure, P_{es} = esophageal pressure, P_b = balloon pressure and P_A = alveolar pressure.

In addition, as an independent confirmation, the final depth of the catheter tip was checked against the calculated distance from the mouth to the level of the diaphragmatic domes. A modification of Zapletal's formula was used: distance (cm) = length (cm) /5.5 + L, where L = 6 or 9 cm for children below or above one year of age, respectively (16).
The non-depolarizing muscle relaxant was given and the measurements started approximately 15 minutes after induction of anesthesia. Measurements were first made in the supine position in five children and first in the right lateral position in eleven. When supine, the child had the arms along the side of the body and the head supported by a small pillow. In the lateral position, the frontal plane of the child was perpendicular to the operating table. The legs were flexed 90? both at the knee and in the hip joints. The upper (left) arm was flexed 90 ? at the elbow and shoulder and was supported by a pillow. The head rested on a pillow. The set-up was as described for the measurement of airway pressure with the addition of one pressure transducer.

The measurement sequence was as follows. The lungs were insufflated to a pressure of 30 - 40 cmH_2O depending on the age of the child, which was maintained for 2 - 3 s before the computer was activated. The activation resulted in closure of the interrupter for 1 s after which the lungs were slowly deflated through the cyclical opening and closing of the interrupter. The deflation was achieved either manually with a supersyringe or by connecting the system via a resistance to a vacuum reservoir. Deflation continued until airway pressure had reached zero, when the computer stopped the measurement sequence. The time for deflation was 13 - 25 s, which equalled 42 - 80 occlusion cycles. Esophageal pressure was sampled and averaged over the same period as the airway pressure. Lung volume decrement was found as previously explained. The series of volume decrements and corresponding pressures were used by the computer to construct three P-V curves: airway pressure (P_{aw}) versus volume, esophageal pressure (P_e) versus volume and airway pressure minus esophageal (transpulmonary) pressure versus volume. As previously, pressure and volume values were recorded continuously by the ink jet recorder and the data were stored on computer disks. All measurements were made in duplicate.

7.3. CALIBRATION

The performance of the SF_6 analyzer is quite stable and daily calibration of the concentration reading is not necessary. The flow signal was calibrated daily with an accurate reciprocal pump producing a flow of 50 ml/s and volume of 30 ml, or with a graded supersyringe, set at a volume of 0.5 l. Sixty percent oxygen in nitrogen was used. The calibration usually changed less than 1% from day to day. Zero adjustment of the flow signal was made immediately before each measurement and was repeated if the zero level had changed more than 1 ml/s. The pneumotachograph readings were not corrected for variations in composition of the expired gas during deflation from TLC. Neither was compensation made for the small error caused by volume changes due to differences between CO_2 influx and O_2 uptake during the pressure-volume maneuver. The flowmeter of the ventilator was calibrated against wet gas meter during ventilation with nitrous oxide/oxygen (F_{IO_2}=0.35-0.5). The airway pressure signal was calibrated before each measurement, against a 20 cm water column.

7.4. ANALYSIS OF THE DATA

The nomenclature used for lung volumes is originally based on volume achieved in awake subjects. Modification is needed to use this nomenclature during general anesthesia. According to Nunn (17) FRC or EEV is determined by elastic forces and is therefore a convenient point at which to consider the various lung volumes and their subdivision. EEV is the volume at the end of normal expiration when the elastic forces have reached equilibrium. TLC is the

volume of gas in the lungs at the end of maximal inspiration. In awake subjects, TLC is achieved when the maximal force generated by the inspiratory muscle is balanced by the force opposing expansion. RV is the volume remaining after a maximal expiration. RV is governed by the balance between the maximal force generated by expiratory muscles and the elastic forces opposing deflation of lung volume. There is an individual and age variation for the pleural pressures at maximal inhalation and maximal exhalation. As TLC and RV are found at these voluntary pressure extremes in awake subjects, they cannot be defined in the same way during general anesthesia.

In Papers II, III, and IV, TLC was generally assumed to be the volume in the lung at 30 cmH_2O. The volume in the lung at the airway pressure of –20 cmH_2O was defined as RV (18).

EEV was found, as in the awake condition, as the lung volume at 0 cmH_2O of airway pressure. The volume present in the lungs at that pressure is called FRC in Papers I and II.

Other capacities and volume were determined in the same way as in the awake condition.

Inspiratory capacity was therefore the volume difference on the airway P-V curve between 30 and 0 cmH_2O. The expression: “at IC” referred to conditions at P_{aw} = 30 cmH_2O, i.e. at the top of the expiratory P-V curves. Vital capacity was the volume between the airway pressure of ? 20 cmH_2O and + 30 (or 20) cmH_2O (VC_{20} and VC_{30}). Expiratory reserve volume was the volume between EEV and RV.

To analyse age-related changes of the P-V relation, the following factors were defined.

The maximal compliance of the respiratory system (C_{rs}) is the slope of the straight line between the upper and lower curvilinear segments of the airway P-V curve. The slope was found by linear regression, after the operator had defined the end-points of the line. The compliance of the lung (C_{lung}) was found in the same volume interval as C_{rs}. In practice, C_{lung} obtained this way was close to maximum C_{lung}, i.e. to the C_{lung} obtained by looking directly for the maximum slope of the transpulmonary pressure - volume curve. Compliance of the chest wall is not reported. This was because the esophageal P-V curve was sometimes close to vertical, i.e. chest wall compliance would have been close to infinity in some patients, which would have made the interpretation of means and regression equations problematic. Instead, its inverse, chest wall elastance (E_{cw}), was obtained. In order to relate E_{cw} to total respiratory system elastance, the latter was obtained as $1/C_{rs}$.

P and V at C_{rs} = pressure and lung volume at the midpoint of the steepest segment of the curve. These values were chosen to illustrate where C_{rs} was reached in each age group.

P at 25% of C_{rs} ($P_{0.25}$) = the pressure above which the slope (compliance) was less than 25% of C_{rs}. This was obtained by identifying the upper

point on the P-V curve where a line with 25% of maximum slope was a tangent to the curve. The value was chosen to indicate at what pressure the transition between the "plateau" and the more steeply sloping part of the curve occurred in different age groups.
V_{10}, V_{20},V_{30}, *etc.* = the lung volumes at 10, 20, 30, *etc.* cmH_2O of pressure. V_{10} and V_{20} were determined to illustrate the volumes, in relation to TLC, attained in children of different ages.
For the analysis of the effect of growth, the static properties of the respiratory system were correlated to a power of body length (19). In all such regression equations, length was expressed in cm.
A factor of 1.09 was used to convert volume and flow from ATPS to BTPS condition.

8. STATISTICS

To assess the reproducibility of repeated measurement, the coefficient of variation was used. This is defined as: SD/m, where SD is the standard deviation and m the mean. For the case of two observations, the formula translates into: D/(m x ?2), where D is the absolute value of the difference. The method of least squares was used for the linear regression analysis of respiratory measures versus weight, age, and length of the child, as well as for corresponding logarithmically transformed variables. Analysis of variance was used to assess whether regression coefficients were significantly different from zero. Multiple regression analysis was used to assess whether adding factors (e.g. gender or cardiac anomalies) improved the models. Linear correlation coefficients (r) were calculated. For paired data, a two-tailed paired *t* test or Wilcoxon signed rank test was used. Fisher´s exact test was used to compare number of children having CC/EEV >1 in relation to other measurements. In case of obviously alinear relations, Spearman's rank correlation (r_{rank}) was used. Data were presented as mean ± SD unless otherwise indicated. P values less than 0.05 were considered to indicate statistical significance.

9. RESULTS

9.1. PAPER I

The highest age-related correlation was between EEV and a power function of height: EEV = 0.00175 x height$^{2.66}$. EEV correlated to weight was also best symbolized as power function. The ratio of EEV to body weight was 17 ? 4 ml/kg in infants, while the value in children more than 1 yr of age was 24 ? 6 ml/kg. Including CHD and gender as variables of the child did not significantly influence prediction. Neither slopes nor intercept for the regression equations in children with CHD were significantly different from those in normal children.

9.2. PAPER II

The shape of the P-V curve changed markedly during the first year of life, but the lung volume (%TLC) at which maximum compliance occurred remained rather constant (61.5 ? 3.4%) at increasing age. In Fig. 7 the volume at the airway pressures of zero (EEV), 10 and 20 cmH_2O expressed as percent of the volume at 30 cmH_2O (TLC) is related to age. The change was most marked during the first year; thereafter these volumes also decrease, but in a more linear fashion.

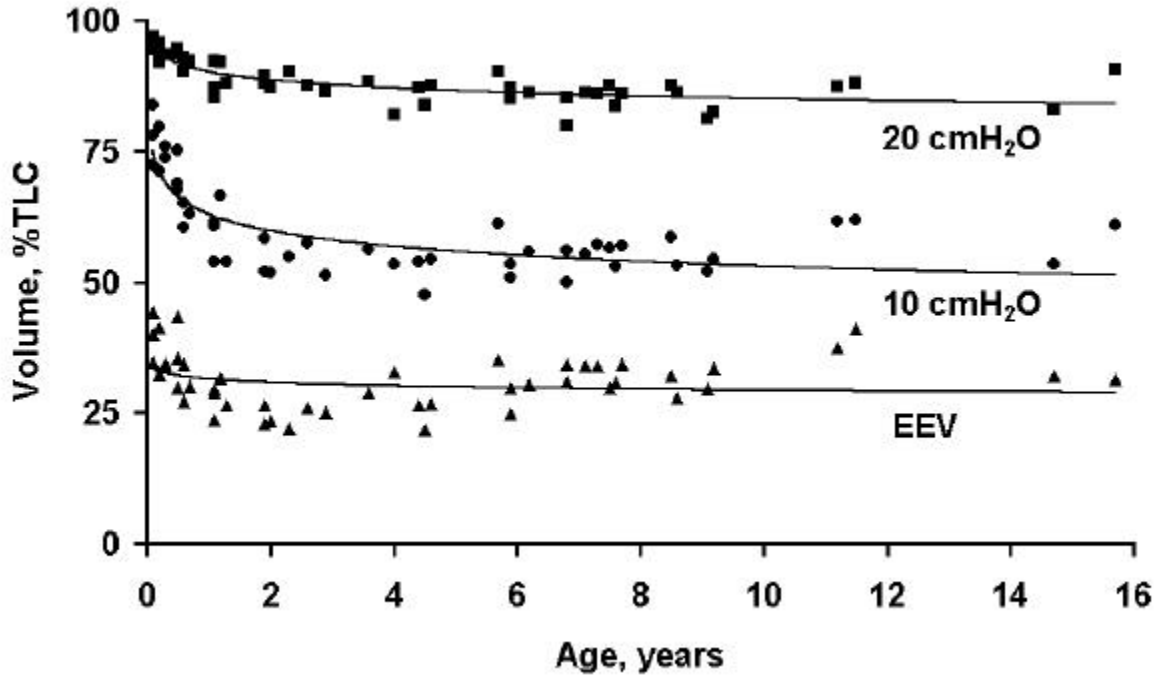

Figure 7. The age related changes of lung volumes at the airway pressure of 20, 10, and 0 (EEV) cmH_2O. The volume is expressed as a percentage of the volume at the pressure of 30 cmH_2O or TLC.

TLC, EEV and compliance of the respiratory system increased with increasing age. This increase was closely related to growth parameters.

However, as the P-V diagram normalized to TLC in younger children was steeper than in older ones, compliance/TLC was actually highest in younger children (Fig. 8 and Paper II, Fig. 4).

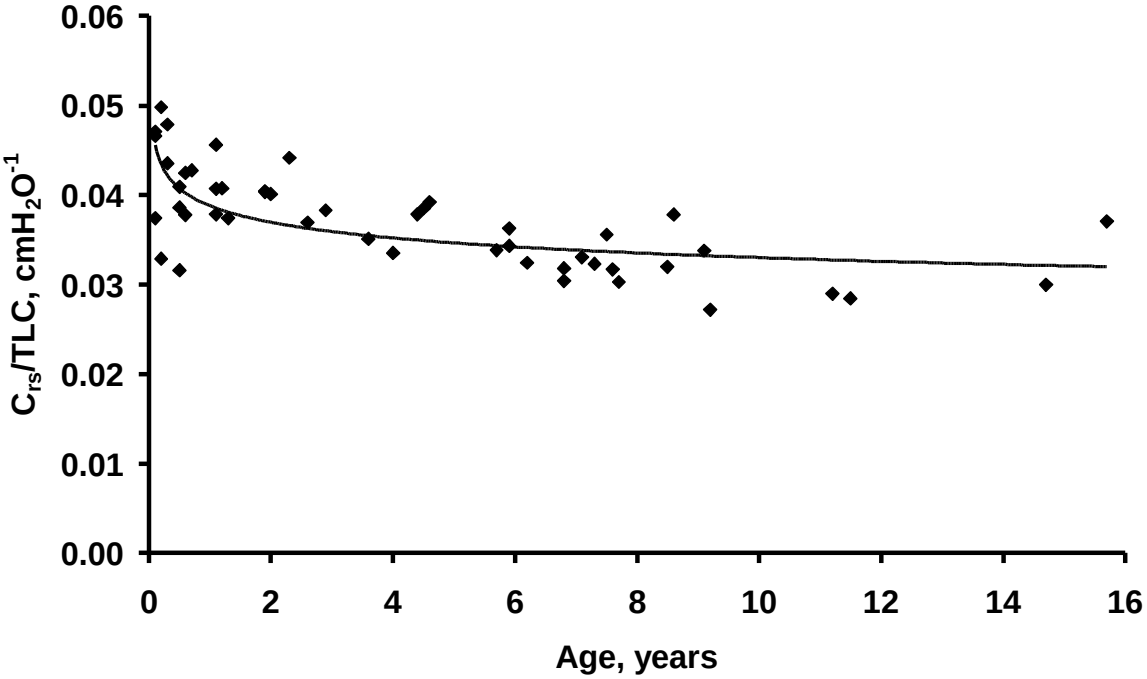

Figure 8. The age-related changes in compliance of the total respiratory system when normalized to TLC.

When the findings were related to weight (Fig. 9A and B), which is clinically a more practical presentation, it was found that all volumes and compliance of the respiratory system was lower in infants (Table II). TLC/weight and C_{rs}/weight increase predominantly up to the age of 5.

Table II. Weight normalized volumes and compliance in infants and older children.

	Infants <0.5 yrs	**Older children >1.5 yrs**
EEV/weight	20 ? 5	26 ? 6
IC/weight	33 ? 9	61 ? 7
TLC/weight	52 ? 13	87 ? 11
C_{rs}max/weight	2.2 ? 0.6	3 ? 0.4

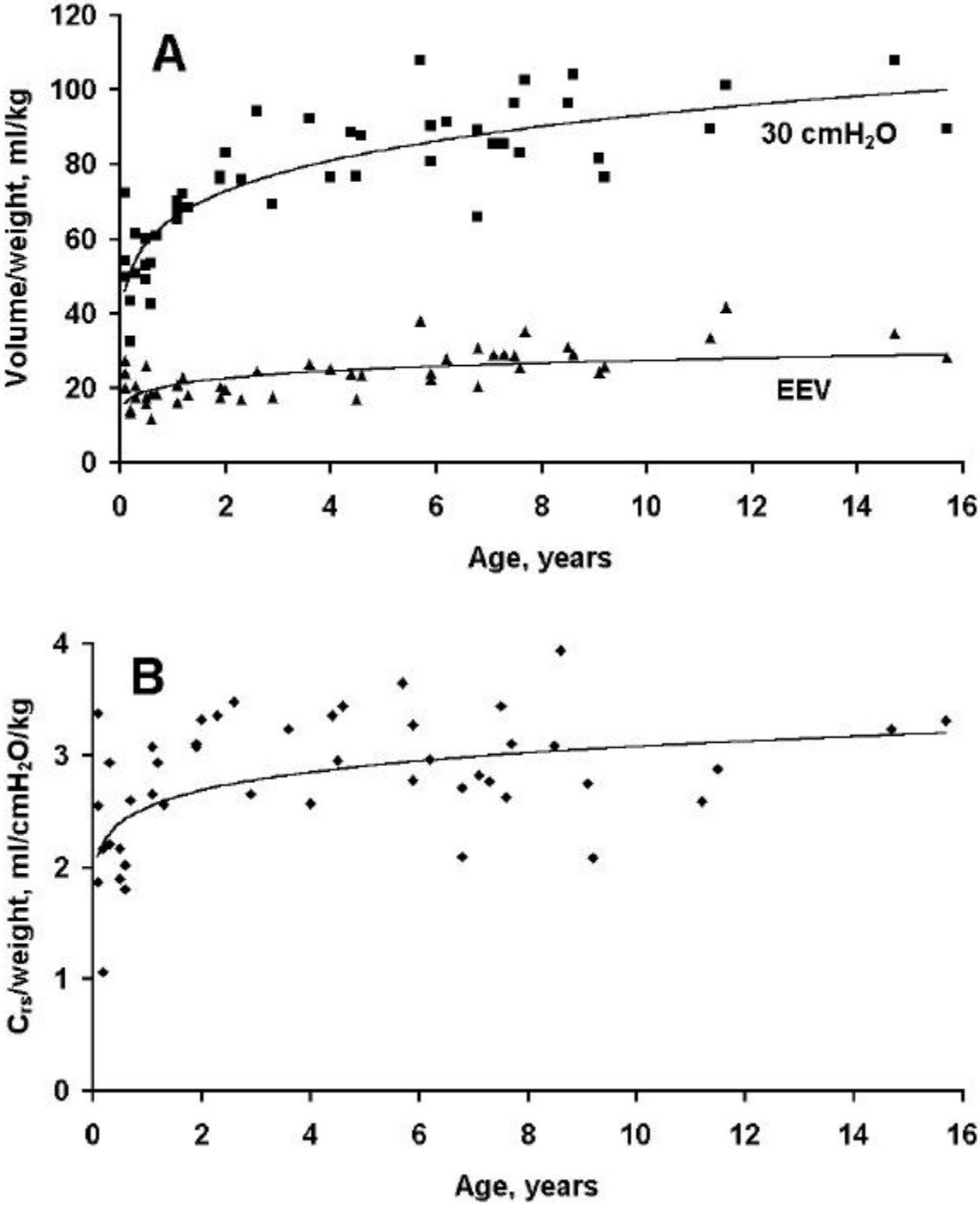

Figure 9. The age-related changes for weight-normalized data. (A) Weight-normalized volume at 30, and 0 (EEV) cmH_2O. (B) Weight-normalized compliance.

EEV as a ratio of TLC was significantly different in infants compared to older children. However, taking the whole group and relating EEV to TLC gave a highly significant correlation (Fig. 10).

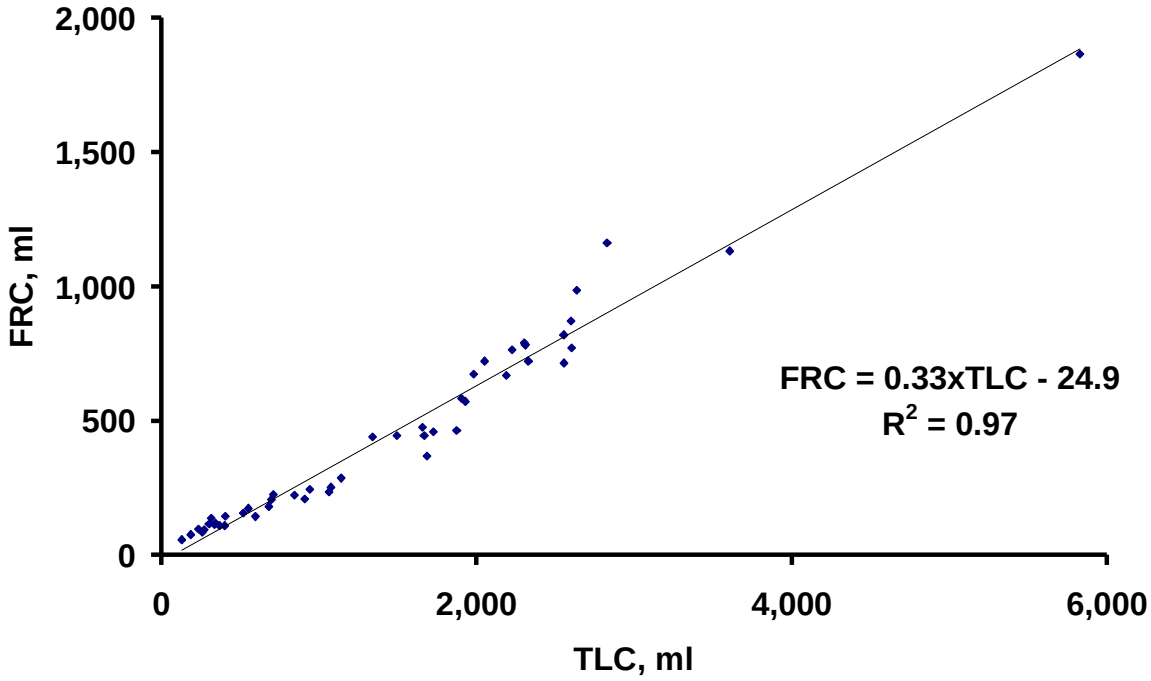

Figure 10. The relationship between EEV and TLC in anesthetized children. During anesthesia the EEV was about 1/3 of TLC.

9.3. PAPER III

It was found that lung compliance, total compliance of the respiratory system and inspiratory capacity increased with increasing age in a regular fashion and that the two latter measures, but not lung compliance, differed widely depending on the body position (supine and lateral). Likewise, there was a substantial difference in the shape of the esophageal P-V curve between the two body positions Paper III, figure 2). Esophageal pressure at EEV was higher, and the Pes-V slope was steeper, in the supine position than in the lateral.

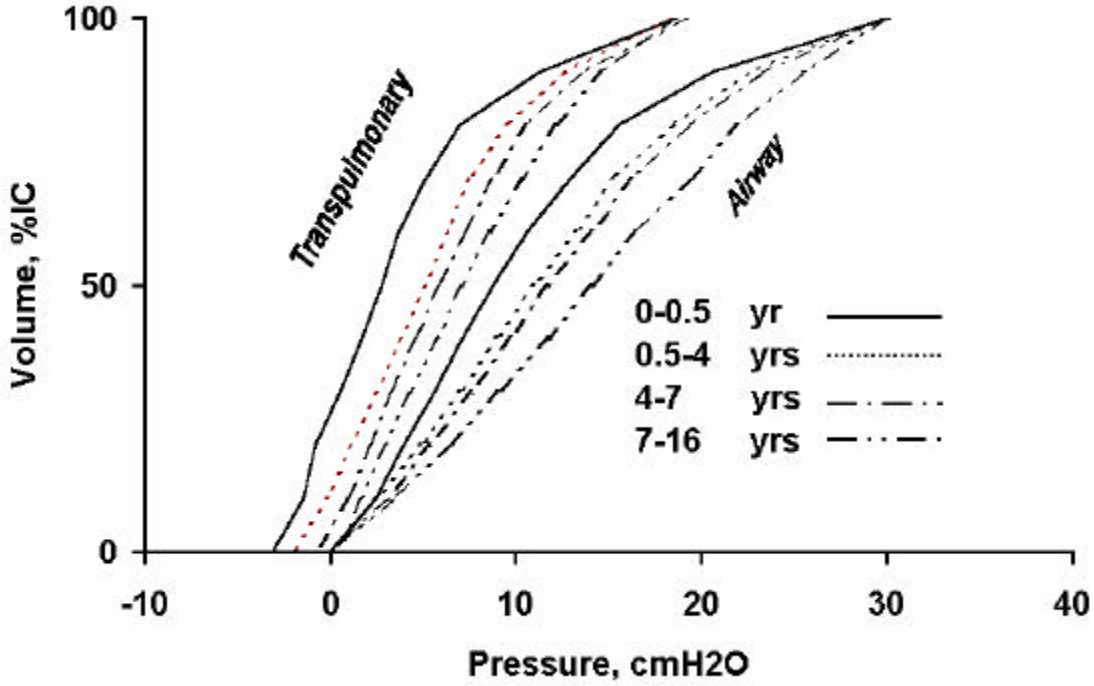

Figure 11. Age grouped airway and transpulmonary pressure - volume relationship. The volume is given as percent of inspiratory capacity. Right lateral position.

In figure 11 the P-V relationship for both the total respiratory system and the lung is shown age grouped (right-sided position). No correction has been made for the difference in pleural pressure and esophageal pressure, which according to (17) is assumed to be 3 cmH_2O in adults. That explains the negative values for the transpulmonary pressure. There was an age-dependent increase in the transpulmonary pressure. Except for the youngest age group, the compliance related to IC seems to be unchanged. The age-related changes for the total respiratory system, which were also found in Paper II, are therefore mostly due to changes in the thoracic wall.

9.4. PAPER IV

Airway closing above EEV occurred in 8 children out of 11 when the ordinary vital capacity maneuver was used. Only 3 children exhibited closing above EEV when lower inflation pressure (20 cmH_2O), typical for ventilator treatment, was used. CC and EEV were both significantly related to age.

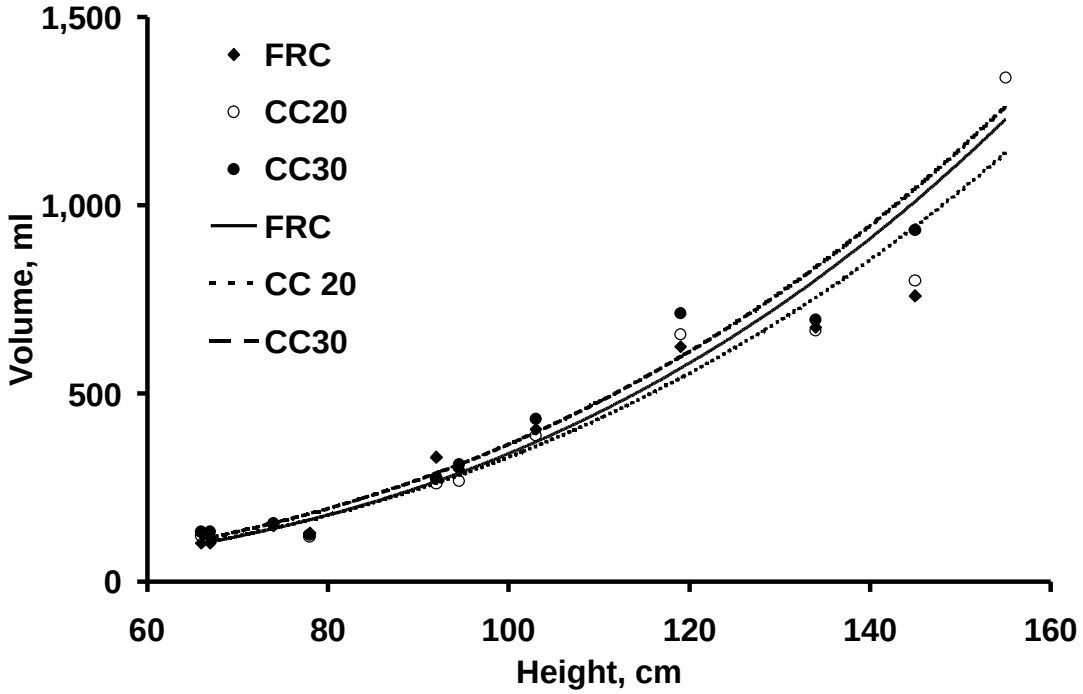

Figure 12. The regression curves for closing capacities (CC_{20} and CC_{30}) and EEV.

In Fig. 12 the regression line for CC_{20} is below, and the regressions line for CC_{30} is above, the regression line for EEV. However, CC values below EEV were not clearly age-related.

9.5. CONSISTENCY OF FINDINGS IN PAPERS I-IV

EEV was measured in Papers I, II, and IV. IC and C_{rs} were measured in Papers II and III. In Paper III the regression lines for IC and C_{rs} were compared to the results in Paper II. The regression lines were very similar.

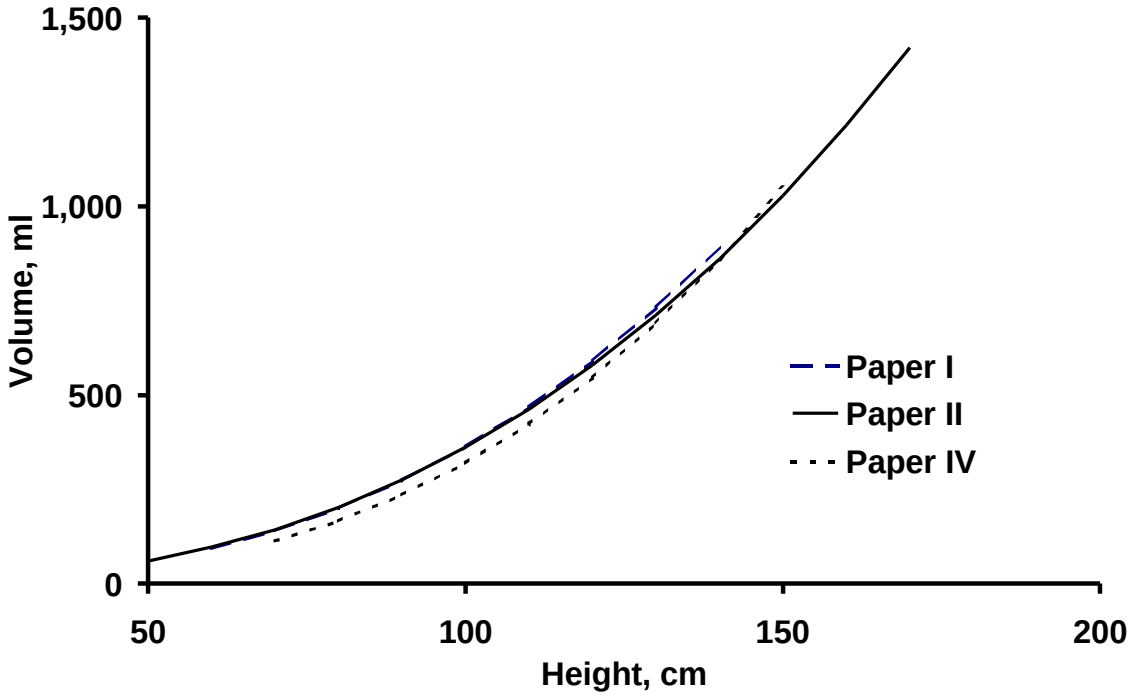

Figure 11. Regression lines for EEV from Papers I, II and IV.

In Fig. 11 it can also be confirmed that the regressions lines for EEV were similar. The regressions line for Paper I is based on both healthy children and children with congenital heart diseases. No measurements made of children in Paper II contribute towards the regression line in Paper I.

10. DISCUSSION

10.1. METHODOLOGY

Three types of measurements were employed in these studies.

- **EEV measurement.**
- **Closing measurement.**
- **Pressure-volume relationship.**

10.1.1. MEASUREMENT OF EEV

The measurement system gave accurate measurements in lung models, and has been shown to yield values in good agreement with nitrogen washout and body plethysmographic techniques in older children and adults (6, 8). The measurement method also gave good agreement with actual volume when using a pediatric-size lung model (Paper I). The measurement technique depends on gas dilution, and may therefore underestimate volume in case of obstructive lung disease. However, none of the patients in the present studies had such diseases. Loss of volume because of air leakage is another potential source of error which was avoided by using cuffed tracheal tubes. In addition, the inspired and expired volumes were monitored, so that leaks could be detected and taken care of. Error due to volume loss is therefore unlikely. Reproducibility was good, with a coefficient of variation of 2 – 3% (Papers I, II, IV), which compares favorably with previous studies in children with nitrogen washout (3.9%) (20) or helium dilution (5.5%) (21).
Dependent atelectasis forms very fast after induction of anesthesisa in almost all children (11, 22) and could also result in misleading information. Recruiting maneuvres and PEEP were used to ensure that the EEV measurement was done in atelectasis-free lungs. It has been shown that atelectasis can be expanded by a recruitment maneuver (sustained inflation of 40 cmH_2O for 15 s in adults) or 5 cmH_2O PEEP for 5 min in children (23, 22). Our strategy of including a few deep breaths before wash-in of SF_6 in children whose lungs were manually ventilated, and using 5 cmH_2O PEEP in children whose lungs were mechanically ventilated, was therefore probably adequate. The PEEP was discontinued 0.5 – 2 min before the end of the wash-in and the lungs were allowed to return to ZEEP condition. The last expiration before washout was also prolonged for the same reason. Residual PEEP volume could be a possibility, but by studying inspired and expired tidal volume after changing from PEEP to ZEEP, we could verify previous findings in adults, in whom the increase in lung volume caused by PEEP is usually gone within five breaths (24).

10.1.2. MEASUREMENT OF CLOSING CAPACITY

Closing was originally measured by the resident gas method (25). This method is based on the difference in nitrogen concentration between dependent and non-dependent parts of the lungs caused by inhalation of pure oxygen. Techniques using a small bolus of tracer gas are usually considered more sensitive than resident gas techniques, because of the larger vertical tracer gradient created within the lung. Hedenstierna *et al.* (18) have shown that use of tracer gas bolus compared to the resident gas method during anesthesia and supine position makes the determination of the onset of phase IV more obvious and makes the coefficient of variation lower, and cardiogen oscillation, which in part reflects the vertical range of concentration, becomes larger. During anesthesia and in the supine position, the vertical lung height becomes shorter and the bolus method, which creates a larger vertical gradient, is therefore more appropriate. The bolus method allows the use of normal concentrations of oxygen and anesthetic gases. Another cause of error, flow dependent closure of airways, is easy to avoid during anesthesia since the rate of airflow is controlled by the investigator.

10.1.3. MEASUREMENT OF PRESSURE-VOLUME RELATIONSHIP

The pressure measured at the airway opening during a condition of zero airway flow was taken to represent alveolar pressure. The occlusion time used was only 0.16 sec which may seem short and in fact a true static condition can not be obtained in such a short time. The time constant needed for equilibrium of the visco-elastic part of the pressure in adults is 0.82 ± 0.11 s, which implies that occlusion of more than 2 s is needed to obtain a true pressure plateau (26). However, the time versus pressure curve in our studies was nearly horizontal during the latter half of each occlusion, indicating that the occlusion time was probably adequate to achieve a measurement eliminating the influence of resistive forces. In order to test whether an occlusion time of 0.16 s was adequate, the interrupter cycle was prolonged to 0.64 s open/0.64 s closed in seven children. The longer cycle made P-V curve somewhat less smooth, but otherwise the curves obtained with the two cycle lengths were similar (Paper II), and C_{rs} and TLC obtained with long cycles were 98 ± 5 % (ns) and 97 ± 2 % ($p < 0.05$) of C_{rs} and TLC obtained with short cycles, respectively.

Also the reproducibility for measures extracted from the P-V curves in Papers II and III (TLC and C_{rs}) was good, as the difference between first and second measurements was only 1 – 2 %. As pointed out above, there is no natural way to define what constitutes a maximal inspiration in an anesthetized patient. We elected to use somewhat reduced inflation pressures in the smallest children. This was because we were afraid of hyperinflating the lungs, particularly of the youngest infants (< 6 months). In these, the thoracic wall is very compliant and

the elastin content of the lungs low. In spite of the reduced inflation pressures, the expiratory P-V curve did exhibit a horizontal plateau in infants. It may be argued that we should have used the same inflation pressure in all children in order to simplify comparison between age groups. However, we felt unable to do so, since pressures that were felt safe in young infants (at most 30 cmH_2O) would be insufficient to expand the lungs fully in older subjects. For example, Rothen *et al.* (27) used an inflation pressure of 40 cmH_2O during vital capacity maneuvers in anesthetized adults. It should be observed that the expiratory P-V curve was always made to start at 30 cmH_2O, at which point TLC was measured. However, this does not fully solve the problem of unequal peak pressures during the foregoing inflation. One point to be noted is that a well-developed upper plateau was obtained in the expiratory P-V curve of all subjects, including the infants.

Measuring the esophageal pressure is the most common way of estimating pleural pressure.

The pressure measured is the sum of the pressures from the surroundings: the tension in the wall of the esophageal balloon, the tonus in the wall of the esophagus, the pressure waves from the beating heart and the weight of the surrounding tissue, i.e. the mediastinum and the abdomen.

This influence on the measured esophageal pressure could even be different at different lung volumes. The lower esophagus is located behind the heart, and it is reasonable that the weight of the mediastinal content should affect the Pes in the supine position, at least at low lung volumes. In the supine position the pressure at EEV was in fact consistently positive (Paper III) raising doubt as to whether esophageal pressure could really be used to represent pleural pressure. However, at higher lung volumes, it is entirely possible that the esophageal pressure curve does provide meaningful information, for example by reflecting variation in pleural pressure with varying lung volume.

10.2. INFLUENCE OF GENDER

In order to achieve sufficient numbers, boys and girls were grouped together. There were more males than females, particularly in Paper III. This may theoretically have skewed the results. There certainly exists a difference in lung volumes between adult men and women even after correction for body size. (28). However, we mainly studied prepubertal subjects and in our material, no significant difference between boys and girls existed, in respect of the various lung function measures.

10.3. THE EFFECT OF ANESTHESIA

The purpose of the studies was to gain insight into the normal respiratory mechanics of children, and it is therefore of interest to investigate to what extent the anesthetic influenced the results.

Halothane is a highly lipid-soluble inhalation anaesthetic and has been found in vitro to alter the surfactant function (29-31). The static properties of the lung are dependent on the surfactant function and it was considered possible that halothane affected the shape of the P-V curves.

The effects of various halothane concentration on EEV and the P-V relation was studied (Ingimarsson et al, unpublished observation). The basal anesthesia was carried out with midazolam and fentanyl infusion and muscle relaxation with pancuron infusion.

Table 3. The effect of increasing concentration of halothane on lung volumes and compliances.

	Volumes			**Compliances**		
Halothane conc.	EEV ml	IC ml	TLC ml	C_{rs} ml/cmH_2O	C_l ml/cmH_2O	C_{tw} ml/cmH_2O
0%	624	1213	1836	55	72	184
0.5%	582	1301	1884	57	74	231
1.0%	589	1318	1908	58	77	216
1.5%	556	1291	1847	59	80	206
<0.15%	601	1285	1885	57	81	173

Values are mean.

The results are shown in Table 3. The study suggested that increasing the concentration of halothane caused a slight reduction of EEV and an increase in chest wall compliance. As a consequence the volume of IC increase and TLC remained unchanged. There was increase in lung compliance (ns). This increase in compliance did not normalize as fast as EEV and was still present when the halothane had been washed out. Thus, there was no evidence that halothane decreased compliance of the lungs, which would have been expected if halothane negatively affected surfactant function. The decrease in EEV may have been the consequence of intrathoracic pooling of blood, reducing the available space for air.

In the studies used in this thesis the children were anesthetized with halothane only, and clinical signs governed the depth of the anesthesia. Usually the end-tidal concentration of halothane needed was 0.5 – 1.0%.

The results of the thesis are therefore not directly applicable to other types of anesthesia, i.e. infusion anesthesia, or the awake state.

10.4. RELATION TO PREVIOUS STUDIES

As mentioned, knowledge of the changes in the lungs during growth is mainly from post mortem studies.

Dunnill (1) found the greatest increase in alveolar numbers to occur during the first 4 years of life and in the size of the alveoli during the first year of life. In the present studies, it was found that the increase in TLC/weight (Paper II, Figs. 3 and 5) occurs mainly during the same time period.

Keeley (2) found that the principal increase in elastin content of the lungs occurs during the first year of life. Also this parallels the findings of the present studies, in which the greatest change in the P-V relations of the respiratory system also occurred during the first year (Paper II). As can be seen in Fig. 5, the lung volume at 10 cmH_2O of airway pressure corresponds to 75% of TLC at birth, while the figure is about 65% of TLC one year later.

In Paper III, respiratory mechanics were analyzed further by separating the contributions from the lungs and chest wall. Fig. 9 shows that the slopes of the age-grouped P-V curves for the lungs are similar except below 0.5 year. The steeper slope in the youngest group depends most likely on lower content of elastin in the lung tissue (2), i.e. the lungs are easier to expand. Our finding agrees also with the previously cited work by Fagan on the P-V relation in excised lungs of infants (3) The decreasing slope for the P-V relation of the total respiratory system after 6 months of age is probably explained by changes in the chest wall component due to, e.g., stiffening of the ribcage and increased gravitional effect from the diaphragm-abdomen.

Our measurements of lung volumes span the period from infancy to the teenage years. Other studies cover either the infancy or older children. Although the TLC estimation during anesthesia was determined by choosing a pre-set inflation pressure, while TLC in the awake subject is defined by the volume at maximal voluntary inspiration, the resulting relation against length was in good agreement with those obtained by others in sitting awake older children and sedated supine infants (32-34). The EEV results were in good agreement with results in supine anesthetized or sedated young children (20, 21, 34). In the case of older children studies of anesthetized children are lacking and the values found in awake sitting children are, of course, higher (32, 33, 37, 38).

Compliance of the total respiratory system is difficult to compare to other studies. Because of the curved lower segment of the P-V curve, the vector compliance starting from EEV found during anesthesia depends not only on the elasticity of the respiratory system but also on how much EEV has decreased during induction of anesthesia. In the awake condition the compliance measured from EEV is usually on the straight segment of the P-V curve. To obtain similar results during anesthesia, a compliance based on the straight segment is therefore more logical. Compliance found by others (37-39) is based on vector compliance measured from EEV in anesthetized children and is

therefore lower than that found by us, while lung compliance presented in Paper III (40-42) shows a good agreement with measurements in awake sitting older children. Studies of younger children and infants are lacking.
Closing data in infants and younger children is totally missing for both anesthetized and awake children. Mansell *et al.* found that the difference between EEV and CC decreased with age in children 6-18 years of age. They observed that in 3 of 9 children below the age of 10 this difference became negative, indicating that there was an airway closure during normal tidal breathing (43). These authors measured closing in awake supine children. Our results during anesthesia show that CC measurement that includes a VC maneuver results in closing above EEV in most of the children. This is not unexpected, as EEV is reduced during anesthesia. The decreased incidence of closing above EEV when inspiratory volume is reduced is in agreement with findings by Holz *et al.* (44) in awake adults and Hedenstierna *et al.* (45) in anesthetized adults.

10.5. CLINICAL IMPLICATIONS

In Papers I and II it was found that the youngest children had the lowest EEV in relation to their weight. This, and the fact that oxygen consumption is also highest in this age group (46), explains the clinical observation that young children becomes hypoxic very quickly (Fig. 12) during induction of anesthesia.

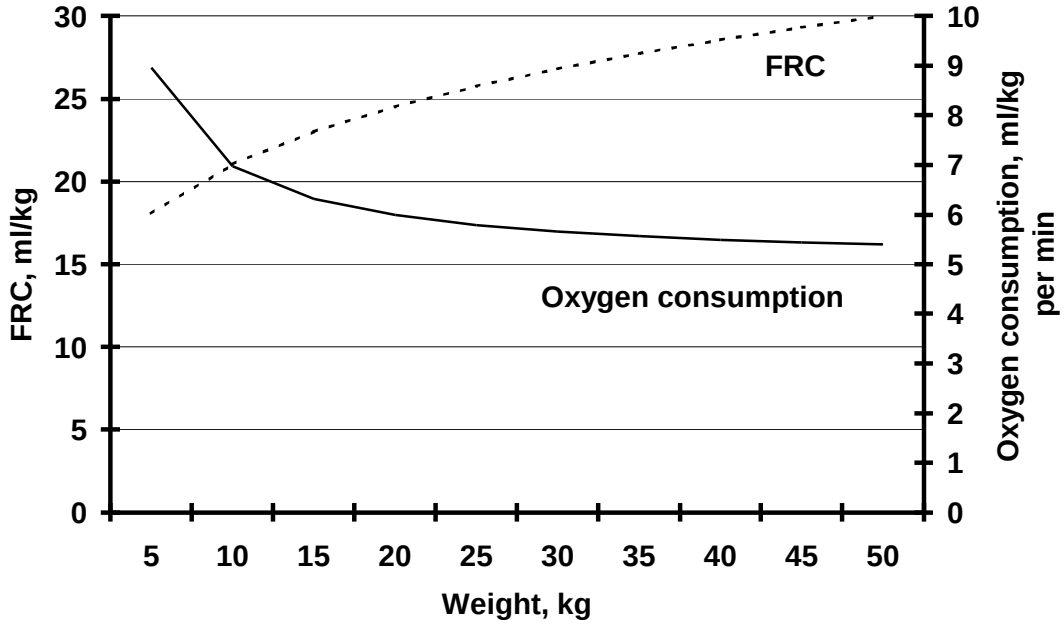

Figure 12. The increase in EEV per kg (Paper II) and decrease in oxygen consumption per kg with increasing weight (46).

Similar EEV was found in healthy children and CHD children without respiratory problems. In this respect, therefore, the latter should behave in the same way as normal children during induction of anesthesia.
The main qualitative changes in the shape of the P-V curve during the first year were found in Paper II. The P-V curve related to TLC in Paper II and to IC in Paper III was steepest in the youngest age group and thereafter the slope declined. A lower distending pressure is therefore needed to hold the lungs open. The steep takeoff from EEV of the TLC-normalized curve in infants implies that a given level of PEEP should have a relatively greater effect on lung volume in these than in older children. Lower PEEP is therefore needed in infants than in older subjects, which agrees with actual practice in ventilated patients.
This difference was examined further in Paper III and by estimating pleura pressure using esophageal pressure registration, the respiratory system was divided in lung and chest wall compartments. Fig. 9 shows that the slopes of the age-grouped P-V curves for the lungs are similar, except in the age group under 0.5 year. The decreasing slope for the P-V relation of the total respiratory system is therefore explained by changes in the chest wall. The steeper slope in the youngest group most likely reflects lower elastin content in the lung tissue. In paralyzed adults, about 50% of the total elastance is attributable to the lungs (17), while according to our results the figure in infants is 90%. Also in the older children of our studies, the contribution from the chest wall did not exceed 70 % of the total. Assessing total respiratory system mechanics, which only requires airway pressure in contrast to the more difficult-to-measure esophageal pressure, therefore gives a reasonably good estimate of the P-V relation of the lungs in the clinical setting, provided the child is relaxed. Furthermore, according to our findings the esophageal pressure recording may be difficult to interpret in terms of pleural pressure, at least in the supine position and at low lung volumes.
Paper IV showed as expected that closing above EEV is a regular phenomenon when a full VC maneuver is used, while closing occurred at lower absolute lung volumes when inflation pressures were reduced. This may have the clinical implication, that lung damage from cyclic opening and closing of airways can be avoided by limiting peak pressure.

11. CONCLUSIONS

These studies have elucidated the changes that occur in lung mechanics during growth.

The following conclusions can be drawn:

- Lung volumes in ml/kg are least in the youngest (Papers I, II and III).
- The greatest qualitative changes in the form of the P-V curve occur during the first year of life (Papers II and III).
- The progressive age-related right-shift of the TLC normalized P_{AW}-V curve, i.e. the curve reflecting the mechanics of the total respiratory system, could be due both to factors in the lung and to factors outside (e.g. stiffening of the chest wall). During the first months – year of life, the change of the Paw-V curve was probably due mostly to changes in the lungs. Thus, the chest wall contributed little (less than 10 %) to total elastance in the youngest subjects. In all children, the chest wall contribution was so low that, in a clinical setting, a good grasp of lung mechanics can probably achieved by simply studying the expiratory P_{AW}-V curve of the tracheally intubated relaxed child. (Papers II and III).
- Closing above EEV occurs at a high rather than a low inflation pressure (Paper IV).

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13. Summary in Swedish

LUNGVOLYMER OCH LUNGMEKANIK HOS BARN UNDER ANESTESI

Avhandlingen är avsedd att fylla luckor i vårt vetande vad gäller normal utveckling av lungvolymer och lungans elasticitet hos barn, från tidiga spädbarnstiden till tonåren. Speciellt har tidigare funnits en brist på data hos barn yngre än skolåldern. Undersökningarna gjordes i narkos och under muskelavslappning.

Mätningar

? Absoluta lungvolymer mättes med en spårgasteknik (utsköljning av svavelhexafluorid).

? Förhållandet mellan luftvägstryck och lungvolym (respiratoriska systemets tryck/volym-diagram) mättes under en långsam utandning med gradvis sjunkande luftvägstryck (3 - 0 kPa).

? I en annan studie gjordes försök att detaljanalysera tryck/volym-diagrammet och särskilja lungans inflytande från det som berodde på tryck från omgivande vävnader. Detta gjordes genom att inte bara mäta luftvägstryck, utan också trycket i matstrupen. Trycket i matstrupen används nämligen ofta hos vakna patienter, för att ge en uppfattning om trycket i lungsäcken.

? I en avslutande studie användes återigen spårgas, nu i ett försök att hitta den punkt under utandningen då luftvägsavstängning börjar uppträda.

Huvudfynd

I. Absolut lungvolym, räknad per kg kroppsvikt, var mindre hos unga spädbarn än hos äldre barn.

II. Den mest uttalade kvalitativa förändringen (alltså med storleksfaktorn eliminerad) i tryck/volym-diagrammets utseende, inträffade under första levnadsåret.

III. I ryggläge förblev trycket i matstrupen positivt även när den långsamma utandningen fortskridit till låga lungvolyme. Trycket steg t.o.m. i vissa fall. När man ändå försökte göra en analys av lungans, respektive omgivande vävnaders betydelse för tryck/volym-diagrammet verkade omgivande vävnader ha liten inverkan (de svarade för cirka 1/10 av lungans inverkan, hos de yngsta).

IV. Luftvägsstängning syntes inträffa vid högre lungvolymer när mätningen gjordes efter en djup föregående inandning (till luftvägstrycket 3, i stället för 2 kPa).

Tolkning av fynden och möjliga kliniska konsekvenser

I. Lungan är alltså mindre, i förhållande till vikten, hos små barn än hos större. Ändå vet vi från andras studier att syrgaskonsumtionen är större. Detta antyder att små barn kan ha minskad förmåga att tåla påfrestningar som tillfälligt avbrott i andningen (som ibland vid inledning av narkos), ökat syrgasbehov (som vid feber), och inskränkningar i lungans möjligheter att expandera (som vid vätska i lungsäcken eller uttalad lunginflammation).

II. Respiratoriska systemet hos unga spädbarn har mindre elastisk återfjädring än hos äldre individer. Detta återspeglar förmodligen ett lägre innehåll i lungorna av ämnet elastin.

III. När lungornas elasticitet skall bedömas hos respiratorbehandlade spädbarn krånglar man oftast bara till det om man försöker renodla lungans och omgivande vävnaders bidrag till respiratoriska systemets totala elasticitet. Man får vanligen en tillräckligt bra uppfattning om elasticiteten i lungorna genom att bara mäta ett tryck vid undersökningen, nämligen luftvägstrycket.

IV. Höga inandningstryck öppnar upp annars sammanfallna luftvägar, som sedan snabbt tycks stänga vid påföljande utandning. Fyndet kan tyda på att stora andetag ger slitskador i lungorna men måste tolkas med försiktighet.

14. Summary in Icelandic

LUNGNARÚMÁL OG LUNGNASTARFSEMI HJÁ SVÆFÐUM BÖRNUM

Tilgangur þessarar doktorsritgerðar var að afla upplýsinga á breytingum sem verða á lungnarúmmáli og lungnastarfsemi barna með vaxandi aldri (0-15 ára). Sérstaklega hefur vantað þessar upplýsingar um börn á aldrinum 0-7 ára. Rannsóknir þessar voru gerðar í svæfingu og vöðvalömun.

Mælingar

? Hvíldarrúmmál (lungnarúmmál í lok venjulegrar útöndunar) var fundið með sporgas aðferð (útskolun á brennisteins hexaflúoríði).

? Sambandið á milli þrýstings í loftvegum og rúmmáls öndunarkerfisins (Þ-R samband) var kannað við hæga útöndun þar sem þrýstingurinn var látinn falla smám saman frá 3-0 kPa.

? Síðan var gerð tilraun til að skipta Þ-R sambandi öndunarkerfisins niður í lungnahluta og brjóstveggshluta. Þetta var gert með því að mæla ekki eingöngu þrýsting í loftvegum heldur einnig í vélinda. Þrýstingur í vélinda hjá vakandi sjúklingi er nefnilega oft notað til að meta þrýsting í fleiðruholi.

? Loks var sporgas aftur notað og núna til að finna þann stað við útöndun þar sem marktæk lokun loftvega byrjar.

Helstu niðurstöður

I. Hvíldarrúmmál miðað við þyngd var minna í ungbörnum en í eldri börnum.

II. Helstu breytingar á Þ-R sambandi öndunarkerfisins varð hjá ungbörnum (áhrif stærðar barns útilokuð).

III. Í baklegu hélst þrýstingur í vélinda jákvæður jafnvel þegar nálgaðist lok útöndunar, gagnstætt því sem vænta mátti og hækkaði jafnvel aftur hjá sumum börnum. Þegar reynt var, þrátt fyrir þetta, að áætla hluta brjóstveggjarins í heildar teygjanleika öndunarkerfisins var hann mjög lítill (1/10 hluti hjá ungbörnum).

IV. Loftvegalokun varð fyrr í útöndun eftir djúpa innöndun (loftvegaþrýstingur 3 kPa í stað 2 kPa).

Túlkun og möguleg læknisfræðileg not

I. Lungun eru minni í ungbörnum en í eldri börnum ef miðað er við þyngd. Samt er þekkt úr öðrum rannsóknum að súrefnisnotkun í hvíld er meiri hjá yngstu börnunum. Þetta leiðir líkur að því að ungbörn þoli verr álag eins og aukna súrefnisþörf (t.d. hár hiti), öndunarstopp (t.d. í byrjun svæfingar) og minnkun á lungnastærð (t.d. brottnám lungnahluta, lungnabólga, fleiðruvökvi).

II. Öndunarkerfi ungbarna hefur minni teygjanleika en öndunarkerfi eldri barna. Þetta stafar sennilega af því að ungbörn hafa lægra innihald af efninu elastini í lungnavefjum.

III. Þegar meta á lungnaástand ungbarna sem eru í öndunarvél er sennilega sjaldnast þörf á að aðgreina Þ-R samband öndunarkerfisins í lungna- og brjóstveggshluta. Það gefur sennilega nægilega skýra mynd af ástandi lungnanna að notast eingöngu við loftvega þrýsting.

IV. Hár innöndunarþrýstingur opnar samfallna loftvegi en þeir lokast aftur snemma við útöndun. Niðurstaða getur bent til að djúp innöndun gefi valdið sliti á lungnavefjum en þetta þarfnast frekari rannsókna.

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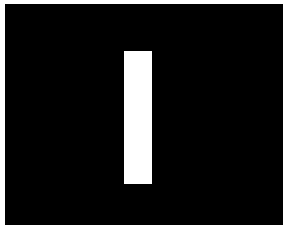
Appendix



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Functional Residual Capacity in Anesthetized Children: Normal Values and Values in Children with Cardiac Anomalies

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To assess the increase in functional residual capacity (FRC) with growth, FRC was measured after induction of anesthesia in two groups of children. One group consisted of 74 children, 0.1–11.2 yr of age, without signs of cardiorespiratory disease (referred to here as "normal" children), and the other of 21 children, 0.2–6.9 yr of age, with cardiac malformations. Anesthesia was maintained with halothane in the normal children and with fentanyl, droperidol, and nitrous oxide in the children with cardiac anomalies. All patients were paralyzed, their tracheas intubated, and their lungs mechanically ventilated. FRC was measured with an automated tracer gas washout technique. In 70 patients the measurements were performed in duplicate with a mean coefficient of variation of 2.0%. FRC correlated significantly with height, weight, and age in both groups. Multiple regression analysis for both groups considered together indicated no significant improvement when factors for the sex of the child or for the presence of cardiac anomalies were incorporated into the model. In normal children the simple linear and nonlinear regression equations for FRC (in milliliters) *versus* height (in centimeters) were: FRC = −529 + 9.48 × height, r = 0.96; and FRC = 0.00175 × height$^{2.66}$, r = 0.97, respectively. The corresponding equations for FRC (in milliliters) *versus* weight (in kilograms) were: FRC = −92 + 29.9 × weight, r = 0.93; and FRC = 9.51 × weight$^{1.31}$, r = 0.95. The ratio of FRC to body weight was lower in normal infants (n = 21) than in normal children above 1 yr of age (n = 53): the values (mean ± SD) were 17 ± 4 and 24 ± 6 ml/kg, respectively ($P < 0.001$). It is concluded that FRC in anesthetized children whose tracheas are intubated can be predicted from height, weight, or age; that the ratio of FRC to body weight was lower in infants than in older children; and that FRC was not affected by the presence of cardiac anomalies. (Key words: Anesthesia: pediatric. Lung: functional residual capacity. Heart, Congenital heart disease.)

IN ANESTHETIZED CHILDREN, airway obstruction and apnea are associated with rapid development of hypoxemia. The smaller the child, the more rapid is the decrease in oxyhemoglobin saturation. Although factors such as the occurrence of intracardiac shunting or airway closure may contribute, the most important factor determining the speed with which hypoxemia develops in healthy children is probably the oxygen reserve contained in the lung and its relation to the oxygen consumption of the child. Knowledge of normal values for functional residual capacity (FRC) therefore is clinically useful. This paper presents results of FRC measurements with a tracer gas washout technique[1–3] in healthy children and in children with cardiac anomalies.

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Methods

PATIENTS

After obtaining approval by the local Human Studies Committee and consent from the parents, 95 children were studied (table 1).

Seventy-four children, 30 girls and 44 boys, were candidates for lower abdominal or urologic procedures and had no evidence of cardiac or respiratory disease. They were regarded as "normal" for the purpose of this investigation.

Twenty-one children, 9 girls and 12 boys, had congenital heart malformations. Six had isolated atrial or ventricular septal defects, and 15 had complex lesions (truncus arteriosus, transposition of the great arteries, double outlet right ventricle, pulmonary atresia, or tetralogy of Fallot). No child had clinical signs of obstructive pulmonary disease, and none required ventilatory support before surgery. The results obtained in 12 of the children with cardiac anomalies have been published previously.[4]

ANESTHETIC TECHNIQUE

In children without cardiac disease, anesthesia was induced with iv barbiturate (n = 59), with iv propofol (n = 2), or with halothane and nitrous oxide *via* face mask (n = 13). All of these children were paralyzed with vecuronium and their lungs ventilated with 1% halothane in air/oxygen (fractional inspired O_2 concentration [$F_{I_{O_2}}$] = 0.6).

In children with cardiac anomalies, anesthesia was induced with iv barbiturate (n = 1), with iv droperidol/fentanyl (n = 8), or with halothane and nitrous oxide *via* face mask (n = 12). Anesthesia was maintained with fentanyl/droperidol, and ventilation was with nitrous oxide/oxygen ($F_{I_{O_2}}$ = 0.35–0.5). Muscle paralysis was accomplished with alcuronium or pancuronium.

In all children, the trachea was intubated with a cuffed endotracheal tube. The cuff was inflated during measurements and the system was checked for leaks by auscultation. The lungs were ventilated with a Servo 900 C ventilator (Siemens-Elema, Sweden) set at volume-controlled ventilation with a constant inspiratory flow, a rate

TABLE 1. Demographic Data

Patients	n	Age (yr)	Weight (kg)	Height (cm)
Normal children	74	2.6 (0.1–11.2)	14 (3.8–36)	92 (52–146)
Children with cardiac anomalies	21	1.5 (0.2–6.9)	8.7 (5.1–22.2)	74 (56–127)

Values are median and range (in parentheses).

of 20–30 breaths · min^{-1}, and a tidal volume of 8–16 ml · kg^{-1}, except in seven of the normal children. In these children the lungs were ventilated with a Mapleson D system, the expiratory limb of which was occluded manually during inspiration. Apparatus dead space varied from 8 ml in the youngest to 38 ml in the oldest, depending on the size of the pneumotachograph and on whether a heat–moisture exchanger was used or not.

MEASUREMENTS

FRC was measured with a multiple-breath washout technique with sulfur hexafluoride (SF_6) as tracer gas. The method has been described in detail previously[1–3]: the tracer gas concentration is measured in the apparatus deadspace with an infrared transducer placed over a cuvette with windows. SF_6 is washed in through a dispensing device, which mixes SF_6 in proportion to the instantaneous inspiratory flow. In this way, a uniform inspired concentration is achieved even with nonconstant inspiratory flow. Wash-in continues until a stable end-tidal concentration of approximately 0.5% is attained. SF_6 washout is started by stopping tracer gas delivery between two inspirations, and is considered complete when the mean expired concentration is less than 0.001%. Signals representing flow and SF_6 concentration are fed into a computer (PDP 11/23, Digital Equipment), which gives an on-line display of inspired and expired tidal volumes and of the tracer gas concentration in each breath, and calculates FRC when washout is complete. FRC is calculated as the volume of SF_6 washed out, divided by the alveolar concentration at the end of the wash-in period. The value is converted to BTPS conditions, and apparatus deadspace is subtracted.

Airway flow was measured with a heated Fleisch pneumotachograph size 00, 0, or 1 connected to a Validyne MP 45 differential pressure transducer (for normal children), or with the standard flowmeter of the ventilator (for children with cardiac anomalies). The pneumotachograph signal was zero-adjusted and calibrated before each measurement with a precision pump using air/oxygen (FI_{O_2} = 0.6). The flowmeter of the ventilator was calibrated against a wet gas meter (Flonic, Schlumberger) during ventilation with nitrous oxide/oxygen (FI_{O_2} = 0.35–0.5). Tidal volume was obtained by integration of the flow signal. The SF_6 analyzer is quite stable, and so daily calibrations of the concentration reading are not necessary. Both the system used in normal children and

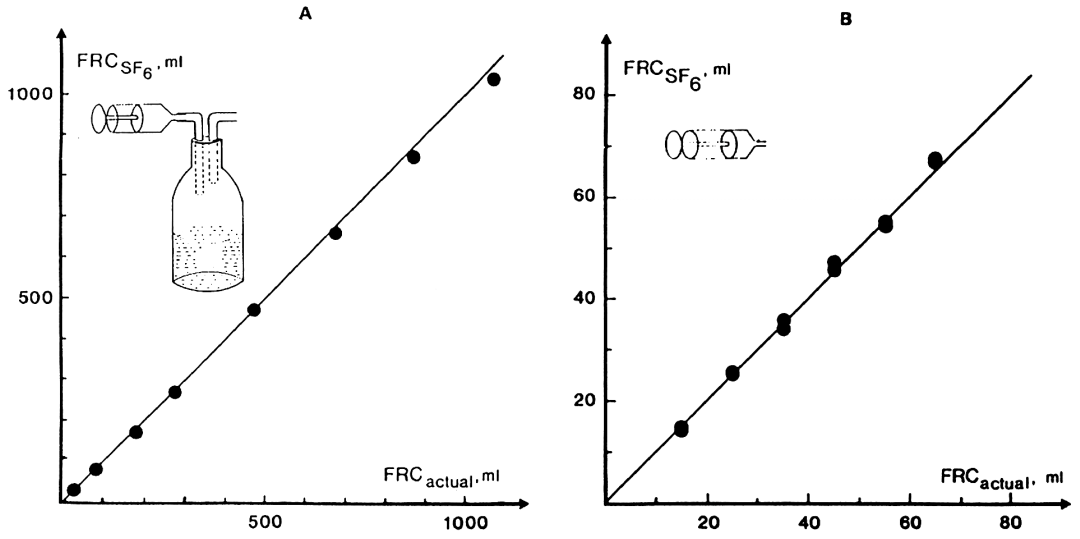

FIG. 1. Performance of the measurement system. (A) Results obtained in a model lung consisting of a 100-ml glass syringe connected to a bottle.[2] The model was ventilated by moving the plunger of the syringe at a rate of 20 min^{-1} and with a tidal volume of approximately 60 ml. (B) Results obtained in a model consisting only of the 100-ml glass syringe. FRC of the syringe was varied between 15 and 65 ml, and ventilation was accomplished by moving the plunger at a rate of 20–30 min^{-1} with a tidal volume of 15–35 ml. Each point represents a single determination. The lines of identity are shown. FRC_{SF_6} = FRC measured with SF_6 washout; FRC_{actual} = FRC of model lung.

the system used in children with cardiac anomalies[4] give accurate measurements in pediatric-size lung models (fig. 1).

Procedure

FRC was measured approximately 15 min after induction of anesthesia in normal children and 30–45 min after induction in children with cardiac anomalies. The measurement was performed prior to surgery and with the patient in the supine position. To control the volume history of the lungs, a few deep breaths were given before wash-in in children whose lungs were manually ventilated, and in most children whose lungs were mechanically ventilated the lungs were expanded with 5 cmH_2O of positive end-expiratory pressure (PEEP) until 0.5–2 min before washout, when the ventilator setting was switched to zero end-expiratory pressure. To ascertain that zero end-expiratory pressure was present during measurement of FRC, flow and tracer gas signals were continuously recorded on paper, and the last expiration was prolonged before tracer gas washout was started.

Statistics

The coefficient of variation for duplicate FRC determinations was obtained as: SD/m, where SD is the standard deviation and m the mean. With FRC as the dependent variable, linear and nonlinear regression equations were calculated for FRC *versus* weight, FRC *versus* height, and FRC *versus* age. Multiple regression analysis was used to assess whether adding factors for the sex of the child or for the existence of cardiac anomalies improved the model. Because log FRC values seemed to be normally distributed and had similar variation around the regression line for different values for the independent variable, this model was used for performing the multiple regression analysis and for testing whether slopes or intercepts were different in children with and without cardiac anomalies. *P* values less than 0.05 were considered statistically significant. Data are presented as mean ± SD unless otherwise indicated.

Results

In 70 of the 95 patients the measurements were performed in duplicate. Duplicate measurements had a mean coefficient of variation of 2.4% (range 0–5.1%) in infants, and 1.9% (range 0–8.5%) in children more than 1 yr of age, giving a mean coefficient of variation of 2.0% for both groups considered together. There was no significant difference between the first and second FRC measurements. The correlation coefficient between the two measurements was 0.999; the slope of the regression line was close to 1.0 (1.002); and the intercept with the y-axis was close to zero (1.25 ml). The 95% confidence limits for individual second determinations were 96.2–106.6 and 498–507, if the first measurements were 100 and 500 ml, respectively.

Normal Children

There was a close correlation between FRC and height, weight, and age (table 2 and fig. 2). As indicated by the

Table 2. Regression Analysis of the Relation of FRC (ml) to Height, Weight, and Age

Relationship	Normal Children, n = 74			Children with Cardiac Anomalies, n = 21		
	A	B	r	A	B	r
X = height (cm)						
FRC = A + BX	−529	9.48	0.96	−289	6.50	0.95
±SEE	34	0.34		40	0.47	
Log FRC = A + BX	1.27	0.012	0.96	1.38	0.011	0.93
±SEE	0.04	0.0004		0.09	0.001	
Log FRC = A + B·logX	−2.76	2.66	0.97	−2.00	2.27	0.94
±SEE	0.15	0.08		0.36	0.19	
X = weight (kg)						
FRC = A + BX	−92	29.9	0.93	−20	24.2	0.93
±SEE	24	1.4		27	2.1	
Log FRC = A + BX	1.85	0.039	0.93	1.86	0.042	0.90
±SEE	0.03	0.002		0.06	0.005	
Log FRC = A + B·logX	0.978	1.31	0.95	1.21	1.12	0.92
±SEE	0.06	0.05		0.11	0.11	
X = age (yr)						
FRC = A + BX	78	83.1	0.96	102	61.4	0.92
±SEE	13	2.6		20	6.0	
Log FRC = A + BX	2.08	0.10	0.94	2.07	0.11	0.88
±SEE	0.02	0.005		0.04	0.10	
Log FRC = A + B·logX	2.27	0.60	0.94	2.26	0.45	0.89
±SEE	0.02	0.03		0.03	0.05	

r = coefficient of correlation; SEE = standard error of estimate.

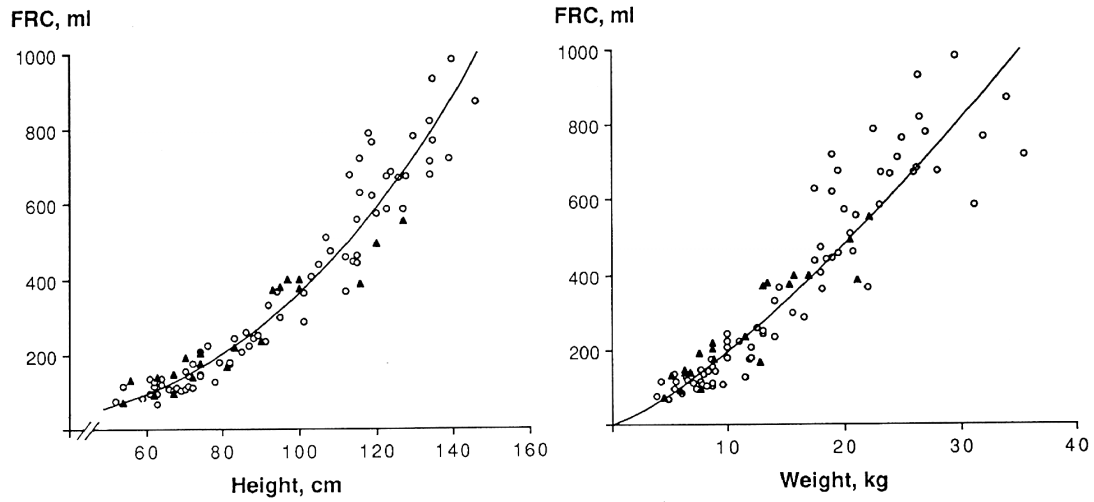

FIG. 2. FRC *versus* height and weight in normal children (circles, n = 74) and children with cardiac anomalies (triangles, n = 21). The regression curves which best fitted the data in normal children are shown (FRC [ml] = 0.00175 × height$^{2.66}$ [cm] and FRC [ml] = 9.51 × weight$^{1.31}$ [kg]).

coefficients of correlation, the increase in FRC with growth was best described by a logarithmic model with height as the independent variable: log FRC = −2.76 + 2.66 × log height, or expressed differently, FRC = 0.00175 × height$^{2.66}$ (where FRC is expressed in milliliters and height in centimeters). Multiple regression analysis indicated no significant improvement when factors for weight or age were incorporated into this model. The simple regression model that best described the increase in FRC with weight also was a logarithmic model (table 2). Thus, the ratio of FRC to body weight increased with age (fig. 3). FRC was 17 ± 4 ml/kg in infants (n = 21), whereas the value in children more than 1 yr of age (n = 53) was 24 ± 6 ml/kg ($P < 0.001$).

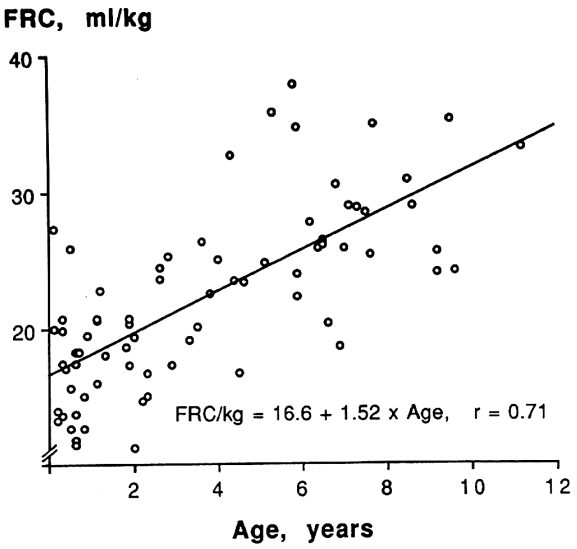

FIG. 3. FRC/bodyweight *versus* age in normal children (n = 74). The equation of the linear regression line is shown.

CHILDREN WITH CARDIAC ANOMALIES

The results are shown in table 2 and figure 2. The increase in FRC with growth was best described by a simple linear regression model: FRC = −289 + 6.5 × height (where FRC is expressed in milliliters and height in centimeters). When using multiple regression analysis for both groups considered together (n = 95), the addition of factors for cardiac disease or for the sex of the child had no significant influence on the regression model. Neither slopes nor intercepts for the regression equations relating log FRC to height, weight, or age in children with cardiac anomalies were significantly different from those in normal children (table 2).

Discussion

METHODOLOGY

The measurement system used is highly automated, gives accurate measurements in lung models (fig. 1), and has been shown to yield values in good agreement with nitrogen washout and body plethysmographic techniques in older children and adults.[1,2] Because the method is based on gas dilution, underestimation may occur in patients who have obstructive pulmonary disease and who have lung units that fill and empty slowly. However, none

of the patients in the current study had such disease. To avoid leaks, the trachea was sealed by the tracheal tube cuff during measurements, and inspired and expired volumes were recorded and compared breath-by-breath in each measurement before it was accepted.

PEEP was applied or a few deep breaths were given before tracer gas washout in order to standardize the volume history of the lungs and to avoid a possible influence of progressive atelectasis. Because of the compliance of the respiratory system of small children, even a small PEEP may increase end-expiratory lung volume markedly; static compliance curves indicate that in a 1-yr-old child, only a few cmH_2O of PEEP may increase FRC by up to 25%.[5] Care therefore was taken to ascertain that the PEEP effect had disappeared and that the last expiration was complete before washout was started. Comparison of inspired and expired tidal volumes in children whose lungs were mechanically ventilated verified previous findings in adults, in whom the increase in lung volume caused by PEEP is usually gone within five breaths.[6] Hence it is unlikely that the use of PEEP shortly before measurements caused an overestimation of FRC. The clinical circumstances did not always allow measurements to be performed in duplicate, but the mean coefficient of variation observed in the current study was only 2.0%, which compares favorably with previous studies in children where nitrogen washout (3.9%)[7] and helium dilution (5.5%)[8] were used. We therefore decided to accept FRC values based on single measurements.

Normal Children

The children without cardiac disease were anesthetized with halothane and paralyzed with vecuronium, and their tracheas were intubated and their lungs ventilated. Previous findings indicate that during halothane anesthesia and tracheal intubation, FRC in children whose lungs are mechanically ventilated is similar to that in children who are spontaneously breathing,[9] but other anesthetic techniques may affect FRC differently. Thus, Dobbinson *et al.* found that FRC in older children was significantly lower after induction of anesthesia with methoxyflurane and intubation than before induction,[10] whereas Shulman *et al.* observed that FRC did not change during induction of anesthesia with ketamine in children who breathed air/oxygen *via* a face mask.[11] Although it seems likely that FRC in children anesthetized with isoflurane or enflurane, for example, would be similar to the values observed in the current study, caution should be exercised in making any further extrapolation.

The regression model that best described the increase in FRC with growth in normal children was a power curve relating FRC to height. To our knowledge, no other group has reported FRC values in relation to weight and height in anesthetized children in whom the trachea is intubated. The shape of the regression curve found in the current study, however, is similar to that observed in previous studies in which gas dilution techniques and a tight-fitting face mask were used to measure FRC (fig. 4). With the exception of the study of Bar-Yishay *et al.*,[8] in which 21 of the 41 children were anesthetized with ketamine, the patients in these studies were either awake or sedated. Bar-Yishay *et al.*[8] and Gerhardt *et al.*[7] studied children 0–8 and 0–5 yr of age, respectively, and found that the increase in FRC with growth was well described by the log FRC to log height relationship shown in figure 4. Gaultier *et al.*‡ studied younger children (0–3 yr) and found a better fit with a linear regression model, with weight as the independent variable. When comparing FRC values predicted by the nonlinear regression equation in the current study ($FRC = 0.00175 \times height^{2.66}$) to those predicted by the equation of Bar-Yishay *et al.* ($FRC = 0.0052 \times height^{2.44}$), who studied a similar age group (only five of our normal children were more than 8 yr of age), our values tended to be somewhat lower, especially in infants. Although it is possible that this difference may be because induction of anesthesia and intubation cause a relatively greater decrease in FRC in infants, as previously suggested by Motoyama *et al.*,§ fur-

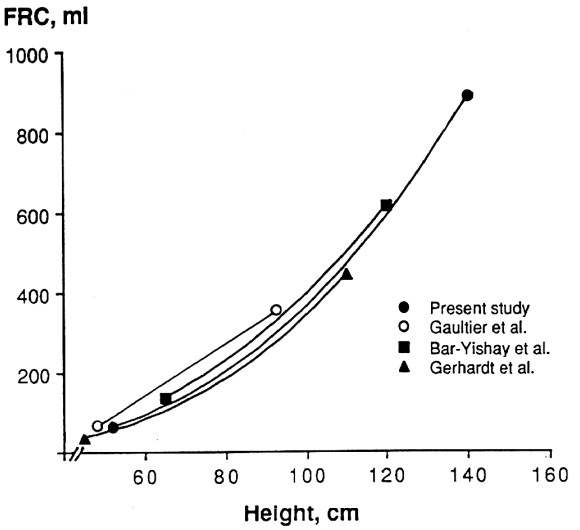

FIG. 4. Regression lines for FRC *versus* height obtained by others in awake/sedated[‡,7] or awake/ketamine-anesthetized children,[8] as compared to the present findings in normal children (FRC [ml] = $0.00175 \times height^{2.66}$ [cm]).

‡ Gaultier C, Boulé M, Allaire Y, Clément A, Girard F: Growth of lung volumes during the first three years of life. Bull Europ Physiopath Respir 15:1103–1116, 1979

§ Motoyama EK, Brinkmeyer SD, Mutich RL, Walczak SA: Reduced FRC in anesthetized infants: Effect of low PEEP. (Abstract) ANESTHESIOLOGY 57:A418, 1982

ther studies in which the same technique is used to measure FRC before and after induction of anesthesia in young children are needed to test this hypothesis. The current finding that FRC values are similar in boys and girls confirms the findings of Bar-Yishay *et al.*[8]

The nonlinear increase in FRC with growth is also apparent when FRC is normalized to body weight (fig. 3). Thus, infants had significantly lower FRC-to-body weight ratios than did older children. This may be of some clinical interest because initial lung volume has been shown to be the most important determinant of hypoxemia during apnea. Findley *et al.*[12] found that apnea of 30 s duration at low lung volumes was accompanied by severe arterial oxyhemoglobin desaturation in awake, healthy adults. At lung volumes below 3,000 ml, corresponding to about 40 $ml \cdot kg^{-1}$, the oxyhemoglobin saturation at 30 s decreased linearly with the decrease in lung volume.[12] Because oxygen consumption in relation to weight decreases with age,[13] while the ratio of FRC to body weight increases with age, it is perhaps not surprising that hypoxemia can occur more rapidly in infants than in older children.

Children with Cardiac Anomalies

Previous studies in awake children[14,15] and in older children during anesthesia[10] indicate that the presence of cardiac anomalies has little effect on FRC if the child does not have congestive heart failure. This seems to be true both for anomalies with and anomalies without increased pulmonary circulation.[4,14,15] Although the current findings appear to confirm that cardiac disease usually does not affect FRC, it should be noted that different anesthetic agents were used in the two groups studied. Also, the measurements in children with cardiac disease were obtained a somewhat longer time after induction of anesthesia, as compared to measurements in normal children.

In conclusion, FRC in anesthetized infants and children in whom the trachea was intubated could be predicted from the weight and height of the child. The prediction did not seem to be affected by presence of cardiac anomalies. When normalized to weight, infants had a lower FRC (in milliliters per kilogram) than older children.

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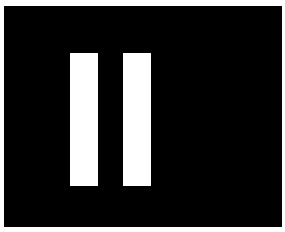

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Pressure-Volume Relations of the Respiratory System in Healthy Children

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Static pressure-volume (P-V) curves of the respiratory system were obtained in 48 healthy children (1 mo to 16 yr of age) during anesthesia and muscle paralysis. The lungs were inflated to a pressure of 25 to 40 cm H_2O, and during the subsequent deflation an interrupter placed in the airway tubing opened and closed every 0.16 s. Airway flow was integrated to obtain the volume decrement between consecutive flow interruptions. Airway pressure was measured during interruptions, and a curve relating pressure to lung volume was plotted, assuming the lung volume at zero pressure to equal functional residual capacity (FRC). FRC was measured using tracer gas washout. The maximum slope of the P-V curve (maximum compliance = C_{rs}max, ml/cm H_2O) was closely related to length (in centimeters) of the child: $C_{rs}max = 7.7 \times 10^{-4} \times length^{2.38}$; r = 0.97. The pressure coinciding with C_{rs}max was 6 ± 1 cm H_2O (mean ± SD) in infants (1 to 6 mo of age) and 12 ± 1 cm H_2O in older children (> 1.5 yr of age). Total lung capacity (TLC) per kg body weight increased with age and was 52 ± 13 ml/kg in infants and 87 ± 11 ml/kg in older children. The FRC/TLC ratio was greater in infants (38 ± 4%) than in older children (30 ± 5%). The lung volume coinciding with C_{rs}max was nearly the same at all ages, when expressed as a percentage of TLC: 62 ± 3%. Specific compliance of the respiratory system, that is, C_{rs}max/TLC, decreased with growth and was 0.044 ± 0.006 cm H_2O^{-1} in infants and 0.035 ± 0.004 cm H_2O^{-1} in older children. It is concluded that although the P-V relations of the respiratory system changed markedly with growth, especially during the first year of life, the lung volume (%TLC) at which maximum compliance occurred varied little. **Thorsteinsson A, Larsson A, Jonmarker C, and Werner O. Pressure-volume relations of the respiratory system in healthy children. Am J Respir Crit Care Med 1994;150:421–30.**

Because of the practical difficulties associated with static compliance measurements in awake preschool children, there are few reports of pressure-volume (P-V) curves in this age group.

Anesthesia and muscle paralysis influence P-V relations (1), and measurements obtained under such conditions can therefore not be compared directly with data in awake children. On the other hand, more standardized measurement conditions are obtained during anesthesia and paralysis than would otherwise be possible, and the data may be useful when caring for mechanically ventilated patients. This paper presents the results of P-V measurements of the respiratory system, that is, lungs and chest wall combined, in 48 children between 1 mo and 16 yr of age. Similar measurements were previously presented by Sharp and colleagues (2), who studied children older than 22 mo and obtained respiratory system compliance (C_{rs}) during deflation from total lung capacity (TLC) by successive volume decrements of 100 to 500 ml. In the present study, however, 20 children were < 2 yr of age, smaller decrements were used by employing computer-governed airway occlusion, and the compliance data were related to absolute lung volumes.

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METHODS

The patients were 20 girls and 28 boys (Table 1) scheduled for lower abdominal or urogenital surgery. None had a history of lung disease or asthma, and physical examination indicated normal lung and heart function. Informed consent was obtained from the parents and from the child, if old enough. The study was approved by the local human studies committee. The measurements were performed before surgery, approximately 15 min after induction of anesthesia, with the patient supine. The P-V measurements were preceded by measurements of functional residual capacity (FRC). Some of the latter results were included in a previous report (3).

Anesthesia and Ventilation

Anesthesia was induced with intravenous thiopental (n = 35), intravenous methohexital (n = 2), intravenous propofol (n = 1), halothane inhalation (n = 9), or rectal methohexital (n = 1). After induction, intravenous succinylcholine was administered, and the trachea was intubated with a cuffed endotracheal tube. The cuff was inflated during measurements to prevent leakage. Anesthesia and paralysis were maintained with 1% halothane in air and oxygen (fraction of inspired oxygen, F_{IO_2} = 0.6) and with a nondepolarizing relaxant, vecuronium, of which 0.1 mg/kg was given shortly before measurements and 0.02 to 0.03 mg/kg 20 min later; three children were ventilated manually in a nonrebreathing system and 45 mechanically with a Servo® 900° C ventilator (Siemens-Elema, Solna, Sweden) set at volume-controlled ventilation, a constant inspiratory flow, a rate of 20 to 30/min, and a tidal volume to give an end-tidal CO_2 pressure of 4 to 5 kPa.

TABLE 1

DEMOGRAPHIC DATA AND RESULTS OF VOLUME AND COMPLIANCE MEASUREMENTS

Patient No.	Age (yr)	Length (cm)	Weight (kg)	Sex	FRC (ml)	TLC (ml)	C_{rs}max (ml/cm H_2O)
1	0.1	47	2.4	M	57.3	130	6.1
2	0.1	52	3.8	M	75.7	189	7.1
3	0.1	54	4.2	F	115	304	14.2
4	0.2	59	6.0	M	83.9	260	13.0
5	0.2	63	7.3	M	96.9	235	7.7
6	0.3	61	5.4	M	94.1	273	11.9
7	0.3	62	5.5	M	114	337	16.1
8	0.5	61	5.3	F	137	318	10.0
9	0.5	68	7.0	M	110	370	15.2
10	0.5	71	8.3	M	144	407	15.7
11	0.6	64	6.5	F	119	346	13.1
12	0.6	70	9.5	M	109	403	17.1
13	0.7	70	8.6	M	157	523	22.3
14	1.1	71	8.5	F	174	554	22.6
15	1.1	74	8.9	F	142	600	27.4
16	1.1	74	10	F	207	700	26.5
17	1.2	75	10	M	225	712	29.0
18	1.3	79	10	F	181	684	25.6
19	1.9	86	11	F	224	845	34.1
20	1.9	85	12	F	208	911	36.8
21	2.0	89	13	F	252	1,077	43.2
22	2.3	91	14	F	235	1,064	47.0
23	2.6	87	10	F	244	942	34.8
24	2.9	101	17	M	287	1,142	43.7
25	3.6	108	18	M	476	1,659	58.2
26	4.0	105	18	F	439	1,339	44.9
27	4.4	112	20	M	458	1,728	65.4
28	4.5	112	22	M	368	1,686	65.0
29	4.6	114	19	M	445	1,668	65.4
30	5.7	116	19	M	722	2,050	69.3
31	5.9	115	18	M	444	1,493	51.2
32	5.9	115	21	M	463	1,874	68.0
33	6.2	126	24	M	668	2,190	71.0
34	6.8	119	25	M	764	2,229	67.8
35	6.8	139	36	M	722	2,330	74.1
36	7.1	122	23	M	673	1,982	65.5
37	7.3	130	27	M	782	2,309	74.6
38	7.5	120	20	M	572	1,930	68.7
39	7.6	123	23	M	584	1,907	60.4
40	7.7	118	22	M	789	2,305	69.9
41	8.5	134	26	F	820	2,554	81.6
42	8.6	134	25	F	714	2,556	96.7
43	9.1	135	32	F	770	2,604	88.0
44	9.2	146	34	F	871	2,600	70.6
45	11.2	140	30	F	985	2,637	76.4
46	11.5	140	28	F	1,162	2,829	80.4
47	14.7	170	54	M	1,866	5,829	175
48	15.7	152	40	F	1,133	3,607	134

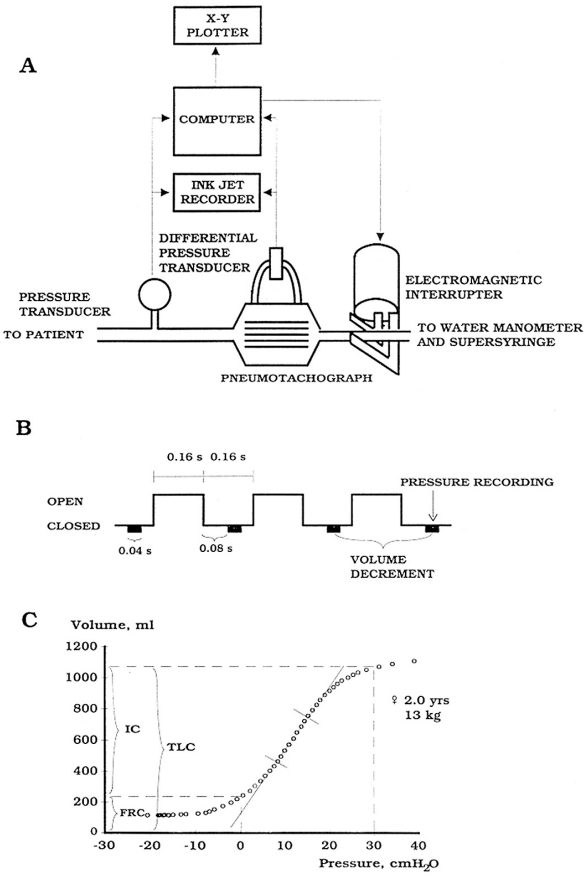

Figure 1. P-V curve construction. (*A*) The P-V measurement system. Arrows represent flow of information. (*B*) The interrupter cycles. The time and duration of pressure and flow (volume) measurements are shown. (*C*) The P-V curve. Each data point represents one interrupter cycle. C_{rs}max was obtained as the slope of a line that best fit the steepest part of the curve. In this tracing (Patient 21), maximum inflation pressure was 38 cm H_2O and C_{rs}max was 43.2 ml/cm H_2O.

Pressure-volume Measurement

The setup (Figure 1A) included a pressure transducer (Druck PDCR-75), a heated Fleisch pneumotachograph (Gould 0 or 1) connected to a differential pressure transducer (MP 45-1-871, range ± 2 cm H_2O; Validyne), an ink jet recorder (EM-81; Siemens-Elema), a computer (PDP 11/23; Digital Equipment Corp.), an X-Y recorder (HP7470A; Hewlett-Packard), a flow interrupter, a 1- or 3-L supersyringe, and a water manometer. The flow interrupter consisted of an electromagnetic valve placed over a soft rubber connector, both from a Servo ventilator (6395404 and 6343438 E037E; Siemens-Elema). Data from P-V measurements (and from FRC measurements, see later) were stored on computer disks, and flow, volume, and pressure were continuously recorded on the ink jet recorder.

The measurement sequence was as follows. After the lungs were expanded by five to six manual bag inflations (FIO_2 = 0.6), they were inflated with the syringe (also containing 60% O_2) to a pressure of 25 to 30 cm H_2O in children < 1 yr of age and to 35 to 40 cm H_2O in older children. The lungs were kept inflated for 2 to 3 s, and the computer was activated. This resulted in closure of the interrupter for 1 s, after which the lungs were deflated over 15 to 25 s by retracting the plunger of the syringe. Deflation continued until airway pressure reached a preset lower limit of −10 to −20 cm H_2O, when the computer stopped the measurement sequence. During deflation the flow interrupter closed for 0.16 s every 0.32 s (Figure 1B), and 0.08 s after start of occlusion the pressure was sampled during 0.04 s and the mean value taken. To obtain the lung volume decrement during interrupter opening, the flow signal was integrated over 0.32 s. Flow and pressure signals were converted from analog to digital every 10 ms and processed by the computer. The series of volume decrements and corresponding pressures was used to construct the P-V curve (Figure 1C). FRC, measured immediately before P-V measurements, was assumed to coincide with the volume at zero pressure. Inspiratory capacity (IC) was measured at 30 cm H_2O, and TLC was obtained as FRC plus IC. When the first P-V curve was plotted it was inspected, and if a definite upper plateau was not observed, the maximum inflation pressure was increased during the second measurement sequence. If this could be done without unduly prolonging the study, at least two good-quality curves with distinct upper plateaus were obtained in each patient. The curve with the highest maximum inflation pressure was chosen to represent the patient.

The reproducibility of compliance measurements was assessed from the last and next-to-last artifact-free curve. To test whether the 0.16-s flow occlusion was sufficiently long, the interrupter cycle was prolonged to 0.64 s open and 0.64 s closed, and the P-V maneuver was then repeated in seven children. Of these, three were included in the main study and the remaining four were studied only for this purpose.

FRC Measurement

FRC was measured with a multiple-breath washin/washout technique using sulfur hexafluoride (SF_6) as tracer gas (4, 5). The tracer gas was washed in with a dispensing device that mixed the gas in proportion to instantaneous inspiratory flow, so that a constant inspired concentration was achieved. Washin continued until a stable alveolar concentration of approximately 0.5% was attained. Tracer gas washout was then started by stopping the SF_6 infusion between two inspirations. Washout was considered complete when the mean expired SF_6 concentration was < 0.001%. Airway flow was measured as described earlier. Signals representing flow and SF_6 concentration were fed into the computer (see previous section), which provided on-line display of inspired/expired tidal volumes and tracer gas concentration and presented FRC immediately after washout. FRC was obtained by dividing the total volume of SF_6 washed out by the alveolar concentration at the end of the washin period. To reduce atelectasis, which regularly appears during anesthesia (6, 7), the lungs were expanded with a few vigorous manual bag inflations before each measurement. In the last 36 children the lungs were also ventilated with 5 cm H_2O positive end-expiratory pressure (PEEP). PEEP was discontinued 0.5 to 2 min before washout to allow return to zero end-expiratory pressure conditions.

Calibration

The flow signal was calibrated daily with an accurate reciprocal pump producing a flow of 50 ml/s and volume of 30 ml or with a graded supersyringe (Pulmark® I; RNA Medical Corp., Woburn, MA), set at a volume of 0.5 L; 60% oxygen in nitrogen was used. The calibration usually changed < 1% from day to day. Zero adjustment of the flow signal was made immediately before each measurement and was repeated if the zero level changed > 1 ml/s. The pneumotachograph readings were not corrected for variations in composition of the expired gas during deflation from TLC. Neither was compensation done for the small error caused by volume changes due to differences between CO_2 influx and O_2 uptake during the P-V maneuver. The airway pressure signal was calibrated against a 20-cm water column. A factor of 1.09 was used to convert volume and flow from ATPS to BTPS conditions. The SF_6 analyzer is quite stable, and daily calibration of the concentration reading is not necessary.

Measures Extracted from the P-V Curve

C_{rs}max (maximum compliance of the respiratory system) is the slope of the steepest segment of the curve (2, 8). This value was obtained visually by identifying the steep linear part of the P-V tracing (see Figure 1C) and was thought to be a better characterization of the P-V curve than measuring the slope at a certain pressure or volume. As the results show, defining compliance from the volume change between two specified pressures or from the change in pressure during a defined volume excursion would not be very meaningful because of the age-related change in the shape of the curve.

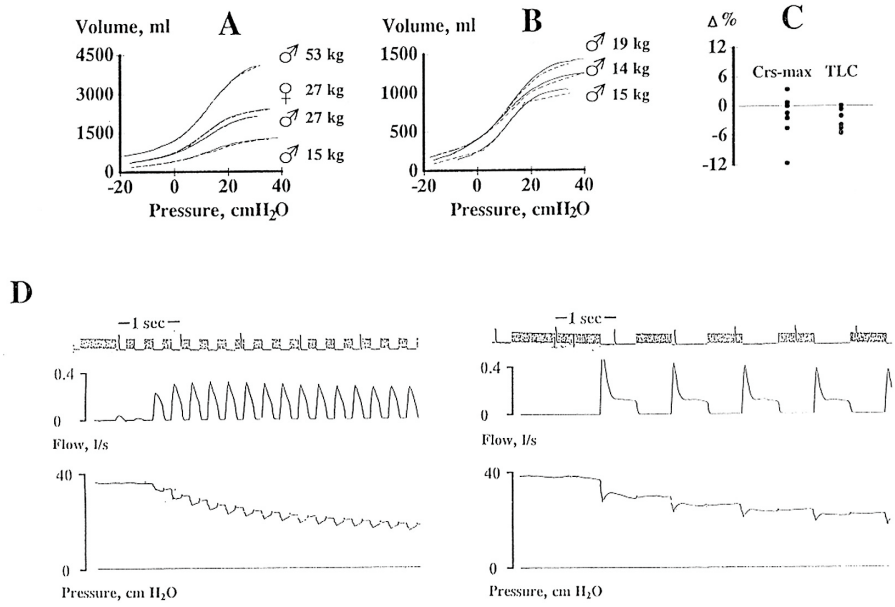

Figure 2. Effect of short (0.16-s) and long (0.64-s) flow interruptions on P-V curves, C_{rs}max, and TLC. (*A* and *B*) P-V curves from seven children in whom both short (*solid line*) and long interruption (*dashed line*) were tested. The two curves obtained in each individual coincide at zero airway pressure because the same FRC value was used to construct both. (*C*) Change in C_{rs}max and TLC when prolonging flow interruptions from 0.16 to 0.64 s. The differences were expressed as

$$\frac{C_{rs}\text{max}(0.64) - C_{rs}\text{max}(0.16)}{C_{rs}\text{max}(0.64) + C_{rs}\text{max}(0.16)} \times 200 \quad \text{and} \quad \frac{TLC(0.64) - TLC(0.16)}{TLC(0.64) + TLC(0.16)} \times 200$$

(*D*) The first parts of recordings during short and long occlusions in Patient 41. The upper tracing indicates when the interrupter was open and closed (*rectangles*). In the far left tracing, the plunger of the syringe was not retracted during the initial two cycles with the occluder open, hence the nearly flat initial flow tracing. The variation in airway flow during the open interval in the far right tracing is caused by flow limitations created by the syringe during manual deflation.

Pressure and volume at C_{rs}max are the pressure and lung volume at the midpoint of the steepest segment of the curve. These values were chosen to illustrate where C_{rs}max was reached in each age group.

Pressure at 25% of C_{rs}max ($P_{0.25}$) is the pressure above which the slope (compliance) was < 25% of C_{rs}max. This was obtained by identifying the upper point on the P-V curve at which a line with 25% of maximum slope was a tangent to the curve. The value was chosen to indicate at what pressure the transition between the "plateau" and the more steeply sloping part of the curve occurred in different age groups.

V_{10}, V_{20}, V_{30}, and so on, are the lung volumes at 10, 20, and 30 cm H_2O of pressure. V_{30} was taken to represent TLC. In the six children in whom maximum inflation pressure was < 30 cm H_2O, TLC was estimated by extrapolation. This was done by studying the transformed variables, 1/V and 1/P (9). The relation between these was nearly linear at pressures above $P_{0.25}$. The equation $1/V = a + b \times 1/P$, where a and b were obtained by linear regression, was used to extend the curve to 30 cm H_2O. The agreement between estimated and measured TLC is reported later. V_{10} and V_{20} were determined to illustrate the volumes, in relation to TLC, attained in children of different ages.

Statistics

The method of least squares was used for the linear regression analysis of respiratory measures versus weight, age, and length of the child, as well as for corresponding logarithmically transformed variables. The influence of gender was tested by stepwise multiple regression, but because it did not significantly improve the prediction of any of the respiratory measures, results from boys and girls are presented together. Linear correlation coefficients (r) were calculated. The significance of linear correlations of paired differences and of differences between age groups was assessed with the two-sided *t* test. The influence of size was also assessed by Spearman's rank correlation (r_{rank}) for some obviously alinear relations. $p < 0.05$ was considered to indicate statistical significance. When not otherwise indicated, values are given as mean ± SD.

RESULTS

Methodologic Assessment

Reproducibility was tested in 22 children, in whom the maximum

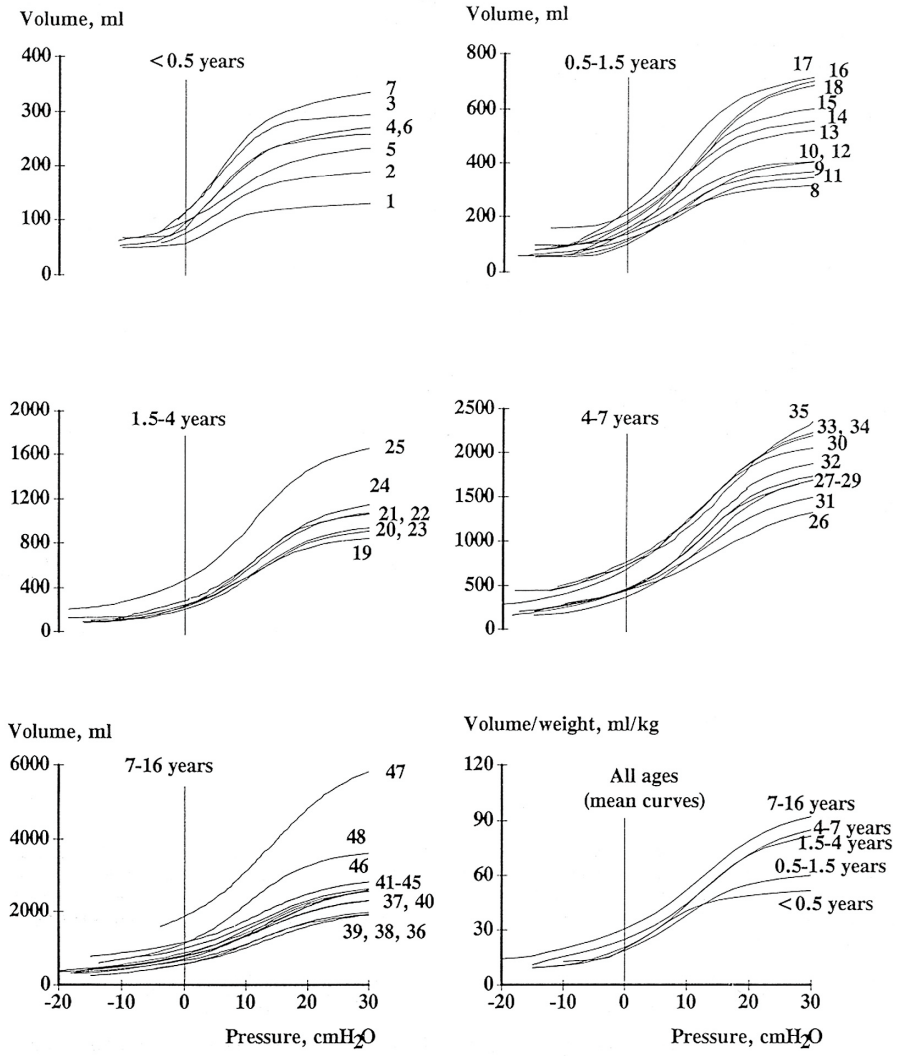

Figure 3. P-V curves in different age groups. The numbers identify the patient (Table 1). In six infants the actual inflation pressure was less than 30 cm H_2O and the P-V curve was extrapolated to this value (*see text*). The lower right shows the weight-normalized mean curves of each age group.

inflation pressures of the next-to-last and last P-V curves were within 5 cm H_2O of each other. The second C_{rs}max and TLC values were 101 ± 6% (not significant, NS) and 102 ± 4% (NS) of the first C_{rs}max and TLC values, respectively. In the 28 children in whom duplicate FRC measurements were made, the second FRC measurement was 99 ± 4% of the first measurement (NS).

The effect of prolonging the flow interruptions during P-V measurements is shown in Figure 2. The resolution of the P-V curve decreased somewhat when using longer opening/occlusion cycles (most obvious in the 15-kg boy in Figure 2B). The C_{rs}max and TLC obtained with long cycles were 98 ± 5% (NS) and 97 ± 2% ($p < 0.05$) of the C_{rs}max and TLC obtained with short cycles, respectively (Figure 2C). Except for a slight decrease in pressure in some patients during the initial, longer occlusion, the pressure-time tracing (Figure 2D) was nearly horizontal during occlusions.

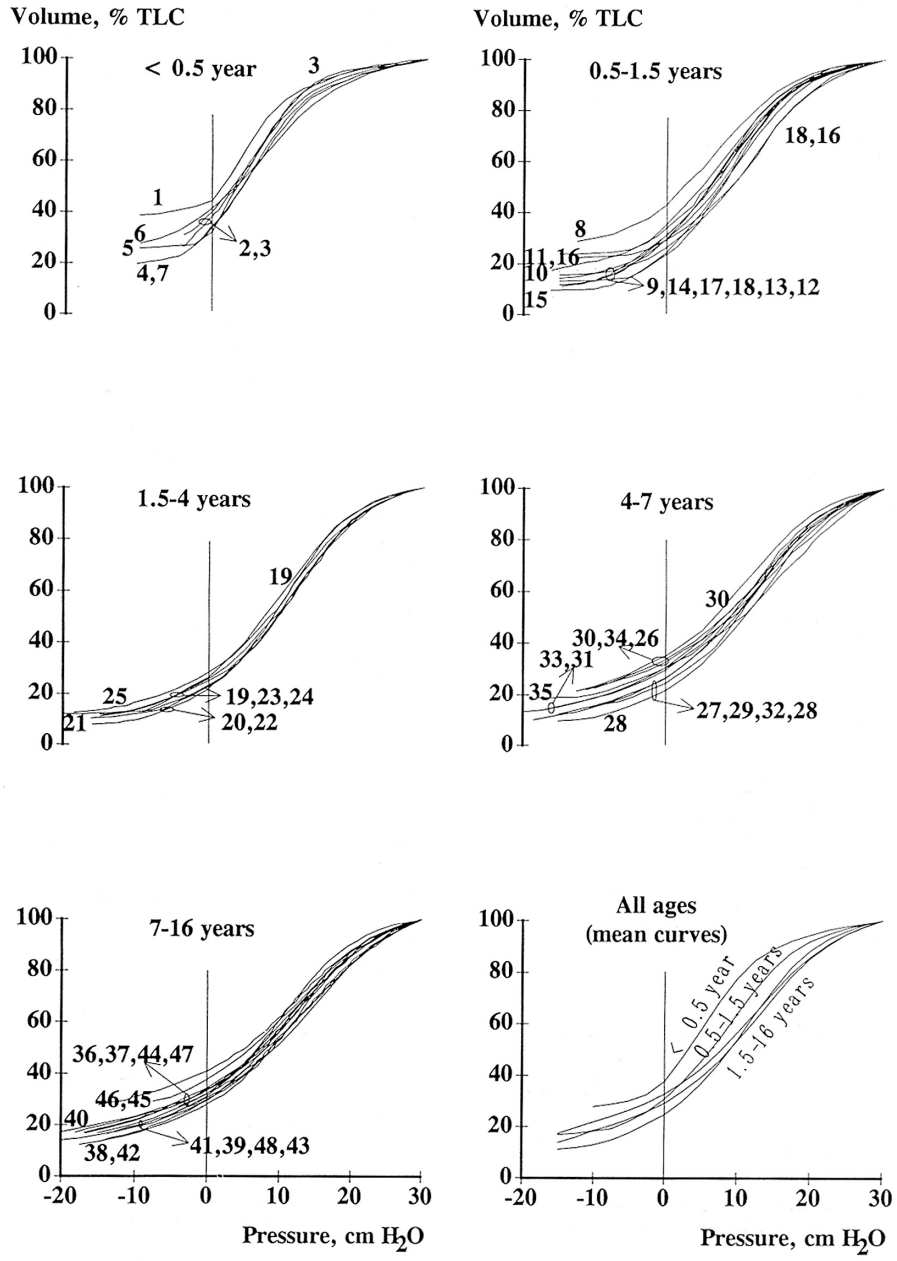

Figure 4. P-V curves normalized to TLC. The numbers identify the patient (Table 1). TLC was defined as the lung volume at an airway pressure of 30 cm H_2O. In six infants in whom actual inflation pressure was less than 30 cm H_2O, the P-V curve was extrapolated to this value (*see* text). The lower right shows the mean curves of each age group.

P-V curve extrapolation to obtain TLC (V_{30}) was done in six children, all < 1.5 yr of age. In these, actual maximum inflation pressure varied between 25 and 28 cm H_2O, with a median value of 27 cm H_2O. In eight patients of similar age in whom 30 cm H_2O pressure *was* reached, measured TLC and TLC extrapolated from 25 cm H_2O (in parentheses) were 272 (273), 239 (240), 309 (310), 289 (290), 325 (330), 440 (444), 497 (499), and 580 (582) ml.

Shape of the P-V Curves

The shape of the P-V curves changed with age (Figures 3 and 4). The changes were most pronounced during the first year of life. When comparing age groups we contrasted findings in infants 1 to 6 mo of age with findings in "older children," that is, those older than 1.5 yr of age.

Cr_{rs}max was closely related to growth parameters. The linear

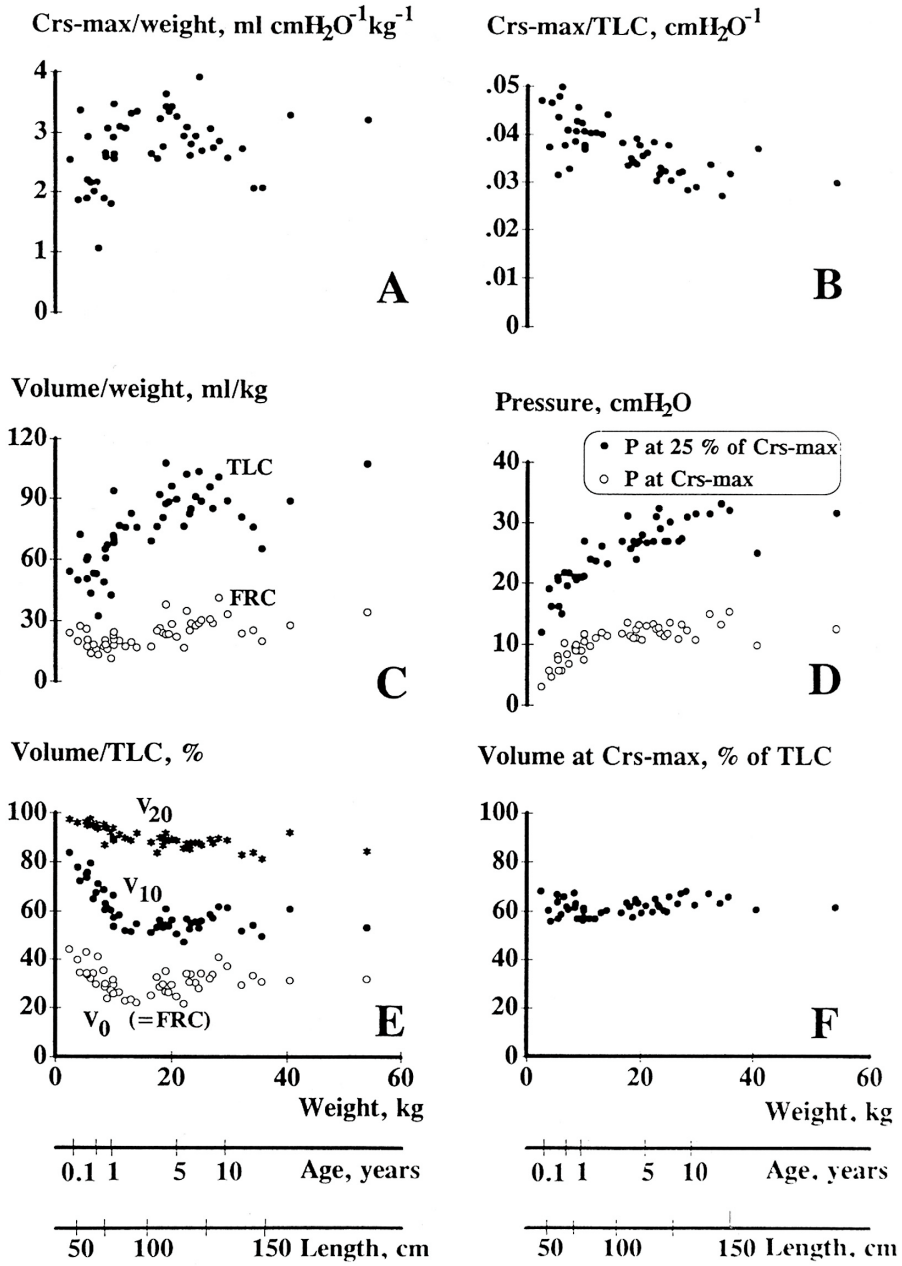

Figure 5. Measures extracted from the P-V-curves. The x axis shows the weight of the child and approximate scales for length and age. The length and age scales were obtained from the following regression equations, derived from the data: log age = −1.964 + 2.008 × log weight, r = 0.97; log length = 1.423 +0.475 × log weight, r = 0.99. V_{10} and V_{20} are the lung volumes at 10 and 20 cm H_2O airway pressure, respectively.

relations for C_{rs}max (ml/cm H_2O) versus length in centimeters and weight in kilograms were C_{rs}max = −52 + 1.03 × length, r = 0.94, and C_{rs}max = −2.5 + 3.02 × weight, r = 0.96, respectively. The greatest value (0.97) was obtained by C_{rs}max = 7.7 × 10^{-4} × length$^{2.38}$.

C_{rs}max/weight (Figure 5A) usually varied between 2 and 3.5 ml/cm H_2O/kg, the mean value being 2.8 ± 0.6 ml/cm H_2O/kg. C_{rs}max/TLC decreased with length, weight, and age (Figure 5B). C_{rs}max/TLC was 0.044 ± 0.006 cm H_2O^{-1} in infants and 0.035 ± 0.004 cm H_2O^{-1} in older children ($p < 0.01$).

C_{rs}max occurred at 5.6 ± 1.4 cm H_2O of alveolar pressure in infants and at 12.2 ± 1.4 cm H_2O in older children (Figures 4 and 5D). The correlation between pressure at C_{rs}max and age was significant (r_{rank} = 0.73; $p < 0.01$). In contrast, the volume at which C_{rs}max occurred in the different age groups was strikingly constant when expressed as a fraction of TLC: 62 ± 3% (Figure 5F).

During deflation, the transition between level and steeper parts of the P-V curve occurred at lower pressure in infants than in older children (Figures 3 and 4). Pressure at 25% of C_{rs}max thus increased with age (r_{rank} = 0.86; $p < 0.01$) and was 17 ± 3 cm H_2O in infants and 28 ± 3 cm H_2O in older children (Figure 5D). The same phenomenon is illustrated in Figure 5E: the lung volume at 10 cm H_2O was 76 ± 4% of TLC in infants and 54 ± 3% of TLC in older children. The upper part of the P-V curve is described in Table 2 in yet another manner: between given pressures, such as 25 and 20 cm H_2O, the relative volume change was greater in older children than in infants.

TLC, FRC, and Inspiratory Capacity

TLC/weight (Figure 5C) increased with growth and was 52 ± 13 ml/kg in infants and 87 ± 11 ml/kg in older children ($p < 0.01$). FRC/weight and IC/weight also increased significantly with growth. Thus, mean FRC/weight was 20 ± 5 ml/kg in infants and 26 ± 6 ml/kg in older children (Figure 5C). Corresponding values for IC were 33 ± 9 and 61 ± 7 ml/kg, respectively. FRC expressed as a percentage of TLC (Figure 5E), however, was greater in infants (38 ± 4%) than in older children (30 ± 5%) ($p < 0.01$).

The linear relations between TLC and FRC in milliliters and weight in kilograms were TLC = −278 + 99.8 × weight, r = 0.98, and FRC = −113 + 32.5 × weight, r = 0.95. As judged by the correlation coefficients, the use of age, length, and/or logarithmic transformation did not improve the prediction of TLC. FRC was best predicted by length in centimeters: FRC = 0.0025 × length$^{2.58}$, r = 0.97.

DISCUSSION

Methodology

We did not want to overinflate the lungs, and lower inflation pressures were therefore used in the infants than in the older children. Because a P-V curve of the respiratory system obtained with a low maximum inflation pressure is not identical to the corresponding segment of a curve obtained with an adequately high pressure (10), these different maximum inflation pressures in children of different ages, rather than true biologic variation, may in theory explain some of the observed differences between the P-V curves in different age groups. The analysis presented in Table 2 indicates, however, that the chosen pressures were sufficient and that further increases in inflation pressure would have yielded small increases in lung volume. For example, the change in volume between 30 and 25 cm H_2O inflation pressure was 1/20 TLC or less in all age groups. It should be recognized, however, that we studied only the expiratory P-V curve, which gives greater volumes at any given pressure than the inspiratory curve because of the hysteresis.

TABLE 2

VOLUME CHANGE (%) BETWEEN DIFFERENT AIRWAY PRESSURES DURING DEFLATION*

Age (yr)	$\frac{(V_{40}-V_{35})\times 100}{V_{40}}$	$\frac{(V_{35}-V_{30})\times 100}{V_{35}}$	$\frac{(V_{30}-V_{25})\times 100}{V_{30}}$	$\frac{(V_{25}-V_{20})\times 100}{V_{25}}$
< 0.5			1.9 ± 0.8 (3)	3.2 ± 1.1 (7)
0.5–1.5		2.2 ± 0.6 (5)	3.3 ± 0.7 (7)	5.4 ± 1.8 (11)
1.5–4		2.4 ± 0.3 (4)	4.0 ± 0.6 (7)	8.2 ± 1.0 (7)
4–7		2.8 ± 0.4 (7)	5.4 ± 1.4 (10)	9.8 ± 1.9 (10)
7–16	2.1 ± 0.4 (5)	3.1 ± 0.5 (11)	5.1 ± 1.1 (13)	9.6 ± 1.9 (13)

* Values are mean ± SD, with the number of observations shown in parentheses. V_{20}, V_{25}, V_{30}, and so on, are the lung volumes at airway pressures of 20, 25, and 30 cm H_2O. V_{30} was taken to represent TLC.

Short (0.16-s) and frequent (every 0.32 s) flow interruptions were used to obtain a P-V curve with high resolution. Our recordings showed that the airway pressure tracing usually became flat almost immediately after interrupter closure. In some children, however, small decreases in pressure were observed during the initial long occlusion (Figure 2D), possibly as a result of stress relaxation or oxygen uptake. The P-V curve was similar, but less smooth, when a longer interrupter cycle was used (Figures 2A and 2B). Hence, the time allotted by the computer for the pressure to stabilize (0.08 s, see Figure 1B) was adequate.

The method used for FRC measurements was previously found to yield good agreement with actual volume in a pediatric model (3). In the present study, FRC obtained during controlled ventilation was taken to represent the lung volume at zero airway pressure in the P-V curve. One possible problem with this approach is that the child was probably free of atelectasis during the P-V maneuver, which was done during deflation from TLC after several previous lung expansions, but not necessarily during the FRC measurement, which included a 2- to 4-min washin period. Indeed, computed tomographic scans show that atelectasis regularly appears in dependent lung regions during anesthesia (6, 7). If atelectasis had been present during FRC measurements but not at zero airway pressure during P-V measurements, this would have had no effect on the shape of the P-V curve but would have caused a downward shift of the curve from its true position. To avoid this possible source of error, the lungs were expanded manually before starting tracer gas washin, and PEEP was used in most patients until shortly before washout. A comparison with previously published FRC measurements (Figure 6A) confirms that FRC is less in the supine than in the sitting position (11–17). Induction of anesthesia and paralysis is associated with a reduction in FRC in older children and adults (18). Although this is not obvious from Figure 6A, our FRC values were indeed somewhat less than those of Bar-Yishay and colleagues (11) and Gaultier and colleagues (12) but slightly greater than those of Gerhardt and coworkers (13). Further studies, in which the same measurement technique is used both before and after induction of anesthesia, are needed to elucidate the effect of anesthesia and paralysis in young children.

Although FRC is affected by posture and state of consciousness, TLC represents a state of "maximum inflation" and should be less influenced by these factors. On the other hand, the slope of the P-V curve is never zero, and the exact value for TLC therefore depends on the inflation pressure at which TLC is measured (Table 2). We chose to define TLC as the volume at 30 cm H_2O inflation because this was simple, the curve was reasonably level at this pressure in all age groups (Figures 3 and 4 and Table 2), and this pressure was reached in most patients. The TLC values

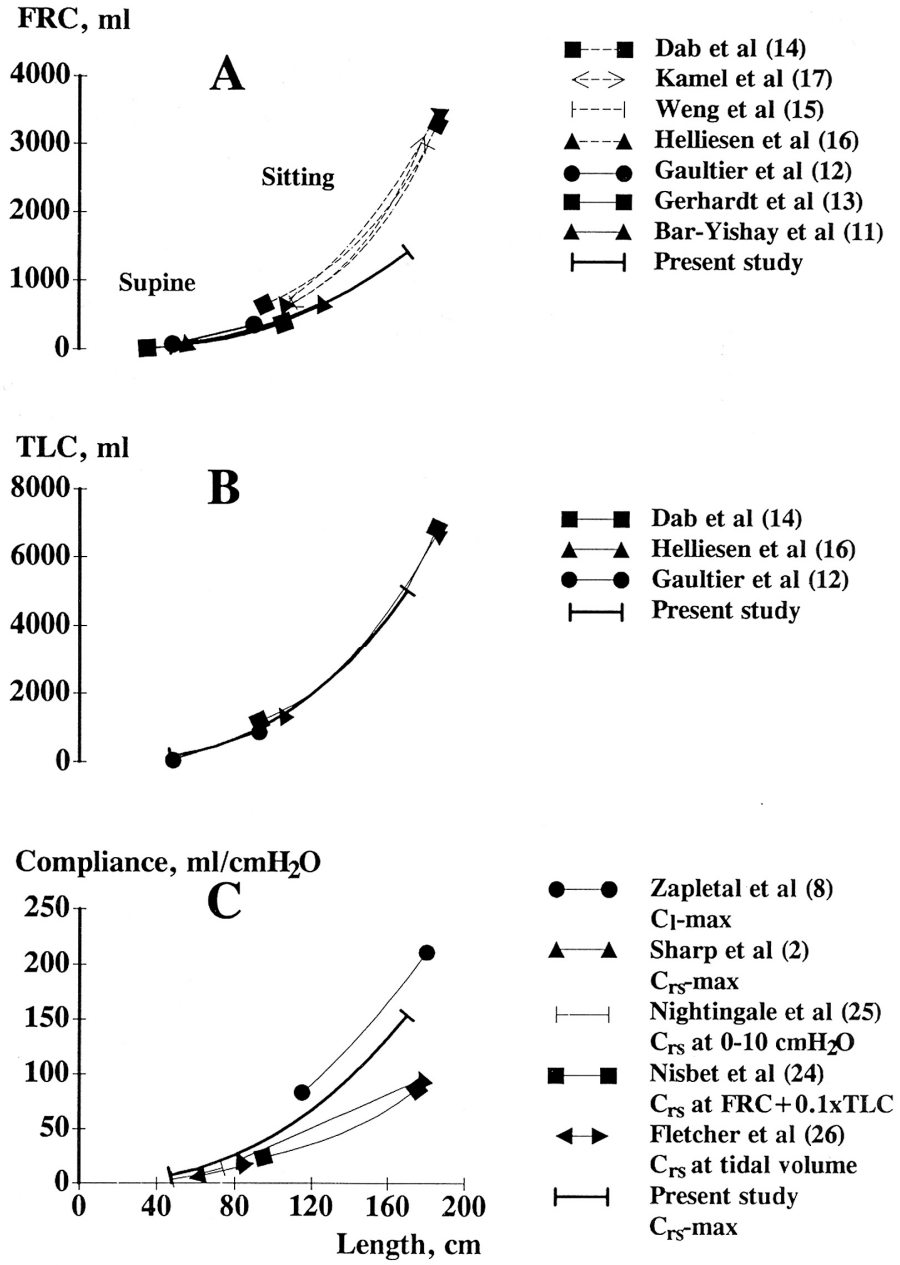

Figure 6. FRC, TLC, and compliance versus length. Comparison with previous studies. Curves of best fit are shown. The relation between the vertical axis (y) and length (x) were of the type $y = ax^b$, except for Dab and Alexander (14), Weng and Levison (15), and Nisbet and colleagues (24) ($y = ae^{bx}$), and for the Gaultier (12) and Sharp groups (2) ($y = a + bx$). The FRC studies were done in awake and sedated children (12, 13), sedated and ketamine-anesthetized children (11), or anesthetized children (present study). The TLC studies were done in awake, sitting children (14, 16), sedated, supine infants (12), or anesthetized, supine children (present study). The different definitions of C_{rs} are explained. The values from the study by Fletcher and colleagues (26) are those obtained during sedated sleep. The C_{rs} values found by these authors during anesthesia and paralysis and ventilation with "high" tidal volumes were not significantly different. For comparison, lung compliance ($C_L$max) obtained by Zapletal and coworkers (8) is also shown. With the exception of the studies by the Fletcher (26) and Zapletal groups (8), the compliance studies were done in anesthetized children.

are in agreement with those obtained by others (Figure 6B) in awake, sitting children (14, 16) and in sedated, supine infants (12).

P-V Relations during Growth

TLC/weight increased with age (Figure 5C); that is, the lung volume was smallest in relation to body volume in young infants. In these subjects, the TLC-normalized P-V curve increased steeply from FRC and leveled off at lower pressures than in older children (Figures 4 and 5D). This agrees with postmortem studies done on excised lungs (19) and is consistent with the finding that the content of "true" elastin in the lungs increases markedly during the first year of life and then remains constant into young adulthood (20). Less elastic recoil of the lungs also explains why young infants had a higher FRC/TLC quotient than older children (Figure 5E), an analogy with the high residual volume observed in older patients who have suffered loss of elastic lung tissue. A decrease in chest wall compliance may be important in older children, but it is less likely that the marked change in the shape of the P-V curve and FRC/TLC ratio in early infancy (Figures 3 through 5) is explained by changes in the mechanics of the chest wall, because its contribution to the elastance of the respiratory system is small in infants (21).

C_{rs}max occurred at approximately 60% of TLC in all age groups. In contrast, the pressure at which C_{rs}max occurred varied. It was only 5 to 6 cm H_2O in infants, but after 2 yr of age this pressure was about 12 cm H_2O. These findings are consistent with reports of an elastic *lung* recoil of 7 to 9 cm H_2O (22) and 5 to 10 cm H_2O (8) at 60% of TLC in children 6 to 18 and 6 to 17 yr of age, respectively. That C_{rs}max/weight (Figure 5A) did not change much during growth can be interpreted as the net result of two opposing tendencies: the amplitude of the P-V curve, drawn with the vertical axis expressed as volume/weight, is smaller in infants (Figure 3) but the TLC normalized curve (Figure 4) is steeper. The observed decrease in C_{rs}max/TLC (Figure 5B) agrees with the finding of Motoyama (23).

The compliance values were closely related to body size. In Figure 6C our C_{rs}max values are compared with results from five earlier studies. There are two important methodologic differences between our study and the studies by Nisbet and colleagues (24), Nightingale and Richards (25), and Fletcher and coworkers (26), explaining why their C_{rs} values were smaller than ours. First, these groups measured inspiratory compliance, which tends to give lower values because of the hysteresis of the P-V curve. Second, they measured "vector compliance," that is, the slope of a line that connects two points on the P-V curve. If the curve between the points does not exactly correspond to the line, it is a mathematical necessity that the slope of the line is less than the maximum slope of the curve. Obviously, vector compliance values based on different volume excursions need not be the same, and Fletcher and coworkers (26) reported a 52% increase in compliance when doubling the tidal volume in ventilated children 1 to 25 mo of age. The difference between C_{rs}max and a vector compliance definition is illustrated in Table 3. When compliance was calculated from the change in pressure between FRC and FRC + 7 ml/kg (normal tidal volume), the resultant values (C_{rs}[1]) were considerably less than C_{rs}max and similar to the values obtained by Nisbet and colleagues (24), Nightingale and Richards (25), and Fletcher and coworkers (26).

Sharp and colleagues (2) used a method similar to that used in our study: they measured total respiratory compliance from the expiratory P-V curve in anesthetized and paralyzed children. This group used greater volume decrements (100 to 500 ml) during P-V measurements than we did. Although this may partly explain their smaller values (Figure 6C), the close agreement between maximum vector compliance (C_{rs}(2) in Table 3), which should be similar to the value obtained by Sharp and colleagues, and C_{rs}max indicates that other differences in methodology may have been important. Sharp's group used a manual technique, reading off the volume decrements from a supersyringe as the lungs were deflated, and the relation of their compliance data to body size (weight and length) was not as close (maximum r = 0.89) as in our study. Our values are more consistent with those of Zapletal and coworkers (8), who measured maximum *lung* compliance (CL-max), that is, the steepest slope of expiratory P-V curves of the lungs, in sitting children and found 16 to 30% greater values than the C_{rs}max values we obtained.

Suter and colleagues (27) advocated the use of compliance measurements to find the "best PEEP" value, that is, the PEEP at which the addition of a tidal volume causes the lowest increase in airway pressure during mechanical ventilation. The corresponding lung volumes and pressures at takeoff of the C_{rs}(2) vector are also shown in Table 3. This pressure was lowest in the infants. The figures could give a rough estimate of best PEEP in various age groups. It should be noted, however, that the pressure at C_{rs}(2) and best PEEP are not identical because the latter value is usually assessed from measurements during inspiration.

The findings may have implications for the care of infants with healthy lungs receiving controlled ventilation. For example, the steep takeoff from FRC of the TLC-normalized curve in infants (Figure 4) implies that a given level of PEEP should have a relatively greater effect on lung volume in these than in older subjects. If inspiratory P-V curves of infants are shifted left in relation to those of older children, as we have found the expiratory curves to be, then increasing the alveolar pressure above, say, 20 cm H_2O has a relatively greater effect on tidal volume in relaxed older children than in infants, an observation that supports the current

TABLE 3

COMPARISON OF VECTOR COMPLIANCES C_{rs}(1) AND C_{rs}(2) AND MAXIMUM SLOPE COMPLIANCE C_{rs}max*

Age (*yr*)	Cr_{rs}max (*ml/cm H_2O*)	C_{rs}(1) (*ml/cm H_2O*)	C_{rs}(2) (*ml/cm H_2O*)	Volume at C_{rs}(2), (*%TLC*)	Volume at C_{rs}(2), (*ml/kg*)	Pressure at C_{rs}(2) (*cm H_2O*)
< 0.5	11 ± 4	9 ± 3	10 ± 3	48 ± 6	25 ± 6	3 ± 2
0.5–1.5	20 ± 7	14 ± 3	19 ± 6	49 ± 7	29 ± 5	6 ± 2
1.5–4	43 ± 9	24 ± 4	39 ± 8	42 ± 3	34 ± 4	7 ± 1
4–7	64 ± 9	36 ± 7	60 ± 11	50 ± 5	42 ± 6	9 ± 2
7–16	88 ± 32	51 ± 18	86 ± 33	51 ± 5	47 ± 6	8 ± 1

* Values are mean ± SD. C_{rs}(1) is the slope of the vector across the P-V curve segment from FRC to FRC + 7 ml/kg (normal VT). C_{rs}(2) is the maximum vector compliance, the slope of the vector across the P-V curve segment in which a volume increase of 7 ml/kg resulted in the smallest increase in pressure. Volume at C_{rs}(2) is the volume at start of C_{rs}(2) vector. Pressure at C_{rs}(2) is the pressure at start of C_{rs}(2) vector.

practice of increasing ventilatory rate rather than pressure in infants in whom minute ventilation must be increased.

In conclusion, the shape of the P-V curve changed markedly during the first year of life, but the lung volume (% TLC) at which maximum compliance occurred remained rather constant during growth.

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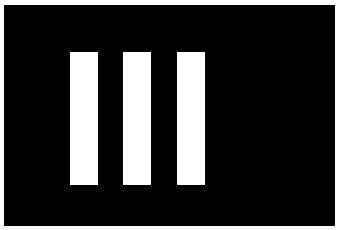

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Lung and Chest Wall Mechanics in Anesthetized Children

Influence of Body Position

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The mechanical behavior of the lung and chest wall has not been determined in preschool children. We therefore obtained static expiratory pressure–volume (P-V) curves of the respiratory system, partitioned into lung and chest wall components using esophageal (Pes) and airway pressure (Paw) registration in 17 anesthetized children (0.2 to 15.5 yr) in the supine and lateral position. From the P-V curves the inspiratory capacity (IC), the chest wall elastance (Ecw), and the maximal compliance of the respiratory system (Crs) and lungs (C_{lung}) were calculated and related to growth. At IC (Paw = 30 cm H_2O), Pes was the same in the two positions: 11 ± 3 cm H_2O. In contrast, at end-expiration (Paw = 0), Pes was close to zero in the lateral position, but markedly positive in the supine position (7 ± 2 cm H_2O). C_{lung} was similar in both positions and increased with growth. Thus, C_{lung} in the lateral position (ml/cm H_2O) = 0.0017 × length$^{2.26}$ (cm), r^2 = 0.90. Crs and IC were approximately 20% greater ($p \leq 0.001$) in the supine position than in the lateral, and correlated strongly ($r^2 \geq 0.93$) with power functions of length in both positions. Ecw expressed as a fraction of total respiratory system elastance (Ecw/Ers) was 33 ± 12% in the lateral position and 12 ± 16% supine ($p < 0.001$). We conclude that the respiratory mechanics in children correlated closely with body size and showed important differences between the supine and lateral positions.

The lung develops considerably during childhood: the relative content of "true" elastin increases markedly during the first year of life and the number of alveoli increases approximately 10 times from birth up to the age of 8 yr, after which lung size increases further owing to alveolar growth (1–3). These changes with age should be reflected in the pressure-volume (P-V) relations of the lungs. However, lung mechanics has only been reported in infants and in children older than 5 yr of age, probably because standardized pulmonary function tests are difficult to perform in awake preschool children. To circumvent this problem, we measured lung and chest wall mechanics during anesthesia and paralysis. When measuring lung compliance (C_{lung}), esophageal pressure (Pes) is commonly taken to represent pleural pressure. However, the Pes–lung volume relation may vary between different body positions. Knowles and coworkers and Ferris and coworkers found that in supine awake adults, the Pes-V curve deviated, below 50% of the vital capacity, toward high pressures in contrast to the corresponding curves obtained in the lateral, sitting, or prone positions (4, 5). On the other hand, van de Woestijne and coworkers were unable to confirm those findings, but instead found a deviation at high volumes in the sitting position (6). Thus, there is a need to learn more about how the Pes-V curve varies between body positions. In recent years, positional change has been increasingly used as a means of improving lung function in mechanically ventilated children and adults with respiratory distress (7, 8). During such maneuvers, Pes may be measured for evaluation of C_{lung}, which emphasizes the need to know the normal shape of the Pes-V curve in different positions—information that is particularly sparse in children.

The aims of the present study were first, to measure C_{lung} and chest wall mechanics from infancy to puberty and second, to investigate and interpret possible differences in Pes-V relations and respiratory mechanics resulting from body position. We performed the measurements with the child in two positions: supine and right lateral.

METHODS

Two girls and fifteen boys (Table 1) 0.2 to 15.5 yr of age, median 2.3 yr, scheduled for urogenital or lower abdominal surgery were studied. None had a history of lung disease and physical examination indicated normal lung and heart function. Informed consent was obtained from the parents and from the child if old enough. The study was approved by the local Human Studies Ethics Committee.

Anesthesia and Ventilation

Anesthesia was induced with intravenously administered thiopental (n = 15) or with halothane inhalation (n = 2). After induction, succinylcholine was administered intravenously and the trachea was intubated with a cuffed endotracheal tube. The cuff was inflated during measurements to prevent leakage. Anesthesia and paralysis were maintained with 1% halothane in air/oxygen (fraction of inspired oxygen [$F_{I_{O_2}}$] = 0.6) and a nondepolarizing muscle relaxant: vecuronium (0.1 mg/kg; n = 13) or atracurium (0.5 mg/kg; n = 4), which was given shortly before the measurements. Electrocardiogram (ECG), end-tidal CO_2, and pulse oximetry (Sp_{O_2}) were continuously monitored. Between and after the measurements the child was connected to a Servoventilator 900C (Siemens-Elema, Solna, Sweden) set at volume control, a constant inspiratory flow, a rate of 20 to 30 min^{-1}, and a tidal volume that gave an end-tidal CO_2 pressure of 4 to 5 kPa.

Measurements

Two sizes of latex balloon catheters, depending on the age of the child, were used for Pes registration; the balloon was 50 or 100 mm long with a diameter of 18 or 36 mm, respectively (when inflated to 5 cm H_2O of pressure). The balloon had good static and dynamic accuracy when tested in its working range (9). After endotracheal intubation and while the child was supine and breathing spontaneously, i.e., before the nondepolarizing muscle relaxant was given, the catheter was passed via the mouth and esophagus into the stomach. The balloon was insufflated with 2 (5) ml air and thereafter exsufflated to a pressure of −5 cm H_2O. A volume of 0.3 (0.8) ml of air was then introduced via a three-way tap to bring the balloon within its working range, and the catheter was connected to a pressure transducer. The pressure in the balloon was registered on an ink-jet recorder (EM-81, Siemens-Elema).

The position of the balloon in the stomach was confirmed by recording a positive pressure during inspiration. The catheter was then

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TABLE 1
DEMOGRAPHIC DATA*

Age (yr)	Length (cm)	Weight (kg)	Sex (F/M)
2.3 (0.2–15.5)	92 (59–172)	13.2 (5.2–56)	2/15

* Values are median (range).

slowly withdrawn until the pressure became negative during inspiration and approximately 3 cm further to clear the balloon of the cardiac sphincter. Correct positioning was confirmed by airway occlusion at end-expiration during spontaneous breathing. If the ratio between the change in Pes and the change in airway pressure (Paw) was in the range 0.94 to 1.00, the position was considered satisfactory, otherwise the position or volume of the balloon was adjusted (9). In addition, as an independent confirmation, the final depth of the catheter tip was checked against the calculated distance from the mouth to the level of the diaphragmatic domes. A modification of Zapletal's formula was used: distance (cm) = length (cm)/5.5 + L, where L = 6 or 9 cm for children below or above 1 yr of age, respectively (10).

The nondepolarizing muscle relaxant was given and the measurements started approximately 15 min after induction of anesthesia. In one child, only supine measurements were made. With the others, measurements were first made in the supine position in five children and first in the right lateral position in 11 children. When supine, the child had the arms along the side of the body and the head supported by a small pillow. In the lateral position, the frontal plane of the child was perpendicular to the operating table. The legs were flexed 90° both in the knee and in the hip joints. The upper (left) arm was flexed 90° in the elbow and shoulder and was supported by a pillow. The head rested on a pillow. The setup has previously been described (11) and includes a computer, a printer, two pressure transducers (SCX01DN; SenSym, Rugby, UK), a heated Fleisch pneumotachograph (Gould 2, Lausanne, Switzerland) connected to a differential pressure transducer (MP 45-1-871, range ± 2 cm H_2O; Validyne, Northridge, CA), a flow interrupter, and a water manometer. The flow interrupter consisted of an electromagnetic valve (closing time 30 ms) placed over a soft rubber connector.

The measurement sequence was as follows. The lungs were insufflated to a pressure of 30 to 40 cm H_2O, which was maintained for 2 to 3 s before the computer was activated. This resulted in closure of the interrupter for 1 s, after which the lungs were slowly deflated, either manually with a supersyringe or by connecting the system via a resistance to a vacuum reservoir. During deflation, the flow interrupter cyclically opened for 0.16 s and closed for 0.16 s, each cycle thus lasting 0.32 s. Deflation continued until Paw had reached zero, when the computer stopped the measurement sequence. The time for deflation was 13 to 25 s, which equaled 42 to 80 occlusion cycles. In order to avoid noise caused by the interrupter itself, to allow it time to close (0.03 s), and to obtain an acceptable pressure plateau, only the pressure signal between 0.08 and 0.12 s after the start of closing the interrupter was processed. The mean Paw value during this period was taken to represent the alveolar pressure during the occlusion. Pes was sampled and averaged over the same period. To obtain the lung volume decrement during each interrupter opening, the flow signal was integrated over 0.32 s from midocclusion to midocclusion. Flow and pressure signals were A/D-converted every 10 ms and processed by the computer. The series of volume decrements and corresponding pressures were used by the computer to construct three P-V curves: Paw versus V, Pes versus V, and Paw minus esophageal (transpulmonary) pressure versus V. In addition, P and V values were recorded continuously by the ink-jet recorder and the data were stored on computer disks. All measurements were made in duplicate.

Analysis of the Data and Statistics

The elastic equilibrium volume (EEV) was defined as the lung volume at 0 cm H_2O of Paw. Because of time restrictions—the studies were not allowed to take more than 30 min of anesthesia time—EEV was not actually measured. In the present report the term is only used to designate the lower end-point of the P-V curves. Inspiratory capacity (IC) was defined as the volume difference on the airway P-V curve between 30 and 0 cm H_2O. The expression "at IC" refers to conditions at Paw = 30 cm H_2O, i.e., at the top of the P-V curves. The maximal compliance of the respiratory system (Crs) is the slope of the straight line between the upper and lower curvilinear segments of the airway P-V curve (Figure 1). The slope was found by linear regression, after the operator had defined the end-points of the line. C_{lung} was found in the same volume interval (Figure 1). In practice, C_{lung} obtained this way was close to maximal C_{lung}, i.e., to the C_{lung} obtained by looking directly for the maximal slope of the transpulmonary pressure–volume curve. Compliance of the chest wall is not reported. This was because the Pes-V curve was sometimes close to vertical, i.e., chest wall compliance would have been close to infinity in some patients, which would have made the interpretation of means and regression equations problematic. Instead, its inverse, chest wall elastance (Ecw), was obtained. In order to relate Ecw to total respiratory system elastance (ERS), the latter was obtained as 1/Crs. For the analysis of the effect of growth, the static properties of the respiratory system were correlated to a power of body length (12). In all such regression equations, length was expressed in centimeters.

Differences between the supine and the lateral position were analyzed for statistical significance by the two-tailed paired *t* test. Analysis of variance was used to assess whether regression coefficients were significantly different from zero. Data are presented as mean ± SD unless otherwise indicated. A factor of 1.09 was used to convert volume and flow from ATPS to BTPS condition.

RESULTS

Shape of the Pes-V Curve

Figure 2 presents mean curves from the whole group of children, in order to convey an overview of the results. Some consistent features could be observed. First, the Pes-V curve was much steeper than the Paw-V curve. Thus, at IC, i.e., at Paw 30 cm H_2O, Pes was only 11.3 ± 2.6 cm H_2O in the lateral position and very similar in the supine position: 11.4 ± 2.6 cm H_2O. Second, Pes at EEV was always distinctly positive in the supine position (6.6 ± 2.2 cm H_2O), whereas on average it was close to zero (1.1 ± 1.9 cm H_2O) in the lateral position. This implies that the Pes-V curve was even steeper in the supine than in the lateral position, as illustrated in Figure 3A, which depicts curves obtained in a 1.2-yr-old boy. Figure 3B, with curves from a 2.5-mo-old boy, shows the same general pattern, i.e., supine and lateral esophageal pressures were similar at IC, whereas Pes at EEV was more positive in the supine than in the lateral position. Pes in this child even increased as lung

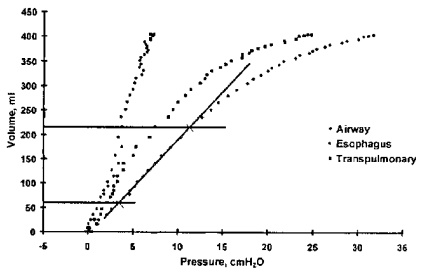

Figure 1. P-V diagrams in the lateral position obtained in a 1.5-yr-old, 80-cm-long boy. Each dot represents an individual occluder cycle. The intersections of the two horizontal lines with the Paw-V curve indicate the points between which the Paw-V curve is nearly linear. The maximal Crs (the slope of the straight line in the figure) was obtained by linear regression on the values between these points. C_{lung} was obtained between the same volumes, from the transpulmonary P-V curve (not shown). Ecw was also obtained in this volume interval, from measurements on the Pes-V curve.

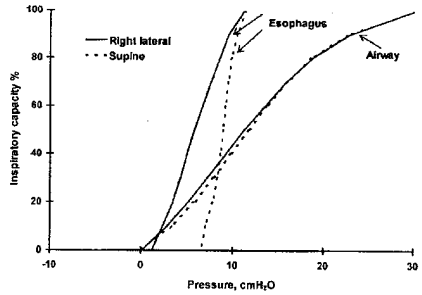

Figure 2. Esophageal and airway pressures versus volume (in percent of IC). Mean curves from the entire cohort of patients are shown.

volume decreased toward EEV. This was seen also in two other children. In three others, Pes did not decrease perceptibly with decreasing lung volume in the lower part of the Pes-V curve.

C_{lung}

As Figure 4 shows, there was a strong correlation between C_{lung} (ml/cm H_2O) and length of the child (cm). Thus, C_{lung} in the lateral position = $0.0017 \times \text{length}^{2.26}$; $r^2 = 0.90$, $p < 0.001$. The values for supine C_{lung} were similar to those seen in the lateral position (Figure 4, Table 2).

Ecw

The supine Ecw values were always less than those obtained in the lateral position (Table 2). Ecw expressed as a fraction of total respiratory system elastance (Ecw/Ers) was 33 ± 12% in the lateral position and 12 ± 16% supine ($p < 0.001$). In the lateral position, the ratio correlated positively but weakly with length ($r^2 = 0.26$, $p = 0.04$). There was no significant correlation in the supine position.

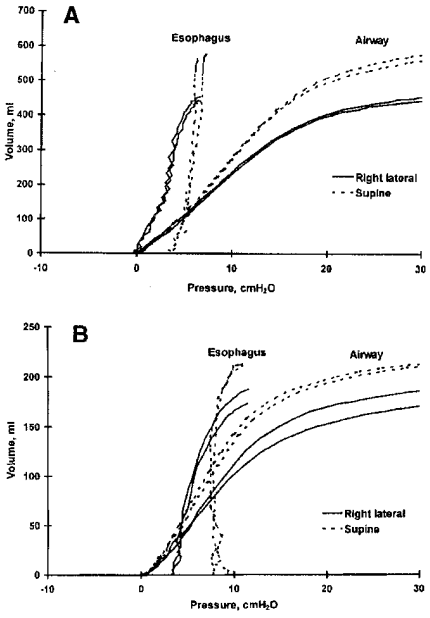

Figure 3. P-V curves from two children. Duplicate curves in the supine and lateral positions are shown. (*A*) Recording from a 1.2-yr-old, 80-cm-tall boy. (*B*) Recording from a 2.5-mo-old, 59-cm-long boy.

Crs and IC

Crs was 23 ± 10% less in the lateral than in the supine position ($p < 0.001$) (Table 2). In both positions, it correlated strongly with growth (Figure 5A). Thus, Crs (ml/cm H_2O) in the lateral position = $0.004 \times \text{length}^{1.97}$ (cm); $r^2 = 0.95$, and Crs in the supine position = $0.0033 \times \text{length}^{2.08}$; $r^2 = 0.93$.

IC was also less in the lateral than in the supine position (by 20 ± 9%; $p = 0.001$, see Figure 5B and Table 2). The equations for best-fit curves with length of the child were: IC in the lateral position (ml) = $0.0083 \times \text{length}^{2.48}$ (cm); $r^2 = 0.96$, and supine IC = $0.0105 \times \text{length}^{2.47}$; $r^2 = 0.97$.

DISCUSSION

It was found that in anesthetized and muscle-paralyzed infants and children: (*1*) Pes at the EEV was higher, and the Pes-V slope was steeper, in the supine position than in the lateral. At IC, Pes was the same in the two positions. (*2*) C_{lung} increased with growth and was similar in the supine and the lateral position. (*3*) IC and Crs increased with growth and were less in the lateral position than in the supine. (*4*) Ecw was approximately one-third of Ers in the lateral position, the ratio correlating weakly with length of the child. The ratio was less (approximately one-eighth) and was unaffected by body size in the supine position.

The cohort included only two girls (1 and 6 yr old) and 15 boys, reflecting the fact that we were studying children operated on in the caudal part of the body, including several boys undergoing hypospadias repair. It is possible that the results were influenced by the gender imbalance. However, in a previous study we could not find any difference in lung volumes and Crs between boys and girls when correction was made for height (11). Also, Lanteri and Sly, who studied 51 children between 3 wk and 15 yr of age, found no influence of sex on inspiratory Crs (13). These comments notwithstanding, there certainly exists a difference in lung volumes between (adult) men and women, even after correction for body size (14). However, we were mainly studying prepubertal subjects (Table 1).

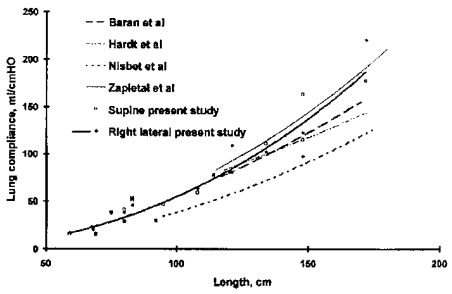

Figure 4. C_{lung} versus length in this and four other studies. The studies by Zapletal (25), Baran and coworkers (26), and von der Hardt and coworkers (27) were done in sitting awake children; the one by Nisbet and coworkers (28) in anesthetized supine children. In all studies, C_{lung} was taken as the steepest slope of the expiratory transpulmonary pressure–volume curve, except for the study by Nisbet and coworkers, in which the slope was found between FRC and FRC + 0.1 × IC. Curves of best fit, relating C_{lung} (ml/cm H_2O) to a function of length of the child (cm), were given by the respective investigators except for Baran and coworkers and Nisbet and coworkers where the curves were constructed by us from their data. The equations were as follows. Baran and coworkers: $C_{lung} = 0.0086 \times \text{length}^{1.909}$, $r^2 = 0.44$. von der Hardt and coworkers: $C_{lung} = 0.081 \times \text{length}^{1.454}$, $r^2 = 0.23$. Nisbet and coworkers: $C_{lung} = 0.0021 \times \text{length}^{2.1319}$, $r^2 = 0.71$. Zapletal and coworkers: $C_{lung} = 0.0043 \times \text{length}^{2.082}$, $r^2 = 0.61$. Present study: C_{lung} in the lateral position = $0.0017 \times \text{length}^{2.26}$, $r^2 = 0.90$.

TABLE 2

WEIGHT NORMALIZED DATA*

	Crs ($ml \cdot cm\ H_2O^{-1} \cdot kg^{-1}$)	IC (ml/kg)	C_{lung} ($ml \cdot cm\ H_2O^{-1} \cdot kg^{-1}$)	Ecw ($cm\ H_2O \cdot ml^{-1} \cdot kg$)
Supine	2.8 ± 0.6	54.7 ± 9.6	3.3 ± 0.7	0.05 ± 0.06
Right side	2.1 ± 0.4	43.6 ± 9.4	3.3 ± 0.9	0.17 ± 0.09

* Values are mean ± SD. Differences between the supine and lateral positions were significant ($p \leq 0.001$), except for C_{lung}.

The measurements were made during anesthesia and muscle relaxation. This entailed at least two potential problems. First, atelectasis forms within minutes of the induction of anesthesia (15, 16). This problem is fairly easily circumvented because the atelectasis can readily be reexpanded by a vital capacity maneuver (17). We therefore inflated the lungs to a pressure of 30 to 40 cm H_2O for 2 to 3 s before each measurement sequence. Second, Ecw during anesthesia and muscle paralysis will be different from that in the awake or lightly sedated state because of loss of intercostal and diaphragmatic muscle activity. Therefore, our results regarding chest wall compliance are only valid in muscle-paralyzed individuals.

We used an interrupter technique to achieve no-flow conditions during the pressure measurement. However, a truly static P-V curve cannot be obtained *in vivo*. When the interrupter is closed, the pressure equilibrates in the lungs and in the airways. In healthy individuals, the equilibration mainly reflects the viscoelastic properties of the lungs, i.e., the stress relaxation of the lung tissues and the alveolar lining (18). Jonson and coworkers found that the viscoelastic time constant in healthy adults was 0.82 ± 0.11 s (18). This implies that an occlusion time of more than 2 s is needed to obtain a "true" pressure plateau. On the other hand, if such long occlusion periods are used, the continuous gas exchange during the prolonged deflation will cause artifacts of the P-V curve (19). We used an occlusion time of 0.16 s, which may seem short. However, the time versus pressure curve was horizontal during the latter part of each occlusion, indicating that the occlusion time was probably adequate. Moreover, in a previous study of paralyzed healthy children, we used the same interrupter technique and in seven of these, we prolonged the occlusion time to 0.64 s (11). The pressure–time curves throughout the occlusions were nearly horizontal, also with the prolonged occlusions, and the Paw-V curves were very similar to those obtained with the shorter occlusion time.

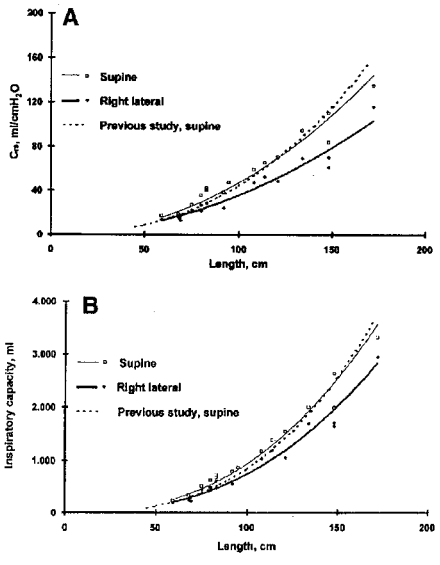

Figure 5. Relation of maximal Crs (*A*) and IC (*B*) to length. The regression equations are given in the text. Comparison with a previous study (11) is made.

Pes, measured by a balloon technique, has been considered to give accurate estimations of the pleural surface pressure in anesthetized adults and children (9, 20). The present study tallies with this finding with respect to the lateral position. Thus, Pes measured in this position decreased smoothly toward zero as lung volume decreased toward EEV. With the child supine, however, a markedly positive Pes at EEV was consistently seen (+7 ± 2 cm H_2O). In three children, part of the Pes-V curve even had a negative slope (an example is shown in Figure 3B). The findings in the supine position are thus difficult to reconcile with the hypothesis that Pes represented an overall pleural pressure. Three possibilities will be discussed, as follows.

Possibility I. The positive Pes at EEV was due to a mediastinal artifact. The lower esophagus is located behind the heart, and it is reasonable that the weight of the mediastinal content should affect the Pes in the supine position, particularly at low lung volumes. Indeed, Knowles and coworkers, and Ferris and coworkers, suggested that there were artifacts caused by the mediastinum on the Pes-V curve at volumes below 50% of vital capacity in the supine position, but not in the sitting, lateral, or prone positions (4, 5). On the other hand, van de Woestijne and coworkers, who studied healthy subjects in the sitting and supine positions, found that the mediastinum caused an artifact in the sitting position at high volumes but not in the supine position (6).

Possibility II. Pes reflected a local pleural pressure. In a study in dogs, Gillespie and coworkers simultaneously measured Pes and the pressure in the pleural space (21). They found that changes in static Pes-V curves with posture (supine, prone, and right lateral) were not caused by mediastinal artifacts. Instead, Pes corresponded to a local pleural pressure obtained in the vicinity, i.e., to pleural pressure at a dorsal site near the diaphragm.

The positive Pes at EEV in our study might be caused by the abdominal pressure, which has a considerable influence on the pleural pressure near the diaphragm (22). Agostino and Hyatt analyzed the effects of gravity on the pleural pressure distribution in the lateral position at FRC in awake humans and found that pleural surface pressure at the upper region of the diaphragm is markedly negative because of the caudal pull of the subatmospheric pressure of the upper, i.e., nondependent abdomen (23). Further down, the abdominal pressure becomes positive owing to the weight of the abdominal contents. This pushes the diaphragm cranially, causing the pressure in the pleura adjoining the diaphragm to be close to zero. If a similar analysis is done of the pressure distribution in the supine position, in anesthetized and paralyzed patients, the pleural surface pressure at EEV may be expected to be slightly

negative in the ventral part but increase and become positive in the dorsal part, owing to the cranial pushing effect on the paralyzed diaphragm caused by the positive pressure in the dependent part of the abdomen. This is approximately 15 cm H_2O in a normal adult (22). Because the lower esophagus lies in the dependent region of the thorax in the supine position and midway between the two sides in the lateral position, the measured Pes at EEV should theoretically be positive in the supine position and approximately neutral in the lateral. The positive Pes at EEV may thus well represent a similarly positive pleural pressure in the dorsal caudal thorax and, hence, a locally negative transpulmonary pressure favoring airway closure and atelectasis (24). In fact, the most common location for atelectasis during anesthesia is in the caudal dependent region of the lung (16, 17).

Possibility III. P-V curves obtained in the supine position did convey meaningful information about global chest wall and lung mechanics. As stated, it is unlikely that Pes in the supine position directly represented an overall pleural pressure, at least not at all lung volumes. This would imply, for example, that transpulmonary pressure at EEV was negative in most parts of the lungs. In spite of this, it is conceivable that the obtained values for Ecw and C_{lung} in our study were, in fact, valid even in the supine position. Thus, they were measured at lung volumes well above EEV, and related changes in P and V to each other—not absolute values. The fact that C_{lung} was the same in the two positions gives some extra support for the thought that the values for supine Ecw and C_{lung} might be valid, and this will be assumed in the following discussion.

To our knowledge, this is the first study reporting *in vivo* static C_{lung} and Ecw in preschool children. C_{lung} in the infants and in the older children agrees with previous studies (25–28) (Figure 4). There was a growth-related increase in the ratio between Ecw and Ers in the lateral position. This might be due in part to an increase in elastance of the abdominal–diaphragmatic component of the chest wall. This component is greatly influenced by the effect of gravity on the abdomen (23). The vertical and lateral distances of the abdomen increase with growth and, because of gravity, this will increase the mean abdominal pressure and thus the contribution to Ecw from the abdomen–diaphragm. However, the increase in the Ecw/Ers ratio may also partly be explained by an increase in elastance of the rib cage caused by the progressive mineralization of the ribs with growth and the increase in the ratio of bone to cartilage (29). The findings are consistent with those by Reynolds and Etsten who found that elastance of the chest wall in relation to total is less in neonates than in adults (30).

Compliance of the total respiratory system was less in the lateral than in the supine position, which tallies with the higher elastance of the chest wall in the lateral position. This might, in turn, have been a consequence of gravity causing a change in the shape of the chest wall. Another line of reasoning also supports our observation of a lower Crs in the lateral position. From studies in adults, it is known that Crs in the middle volume range is higher in the supine than in the upright position (23). The exact mechanism has not been clarified. However, since FRC has been found to be higher in both the lateral and upright positions than in the supine (24, 31, 32), whereas total lung capacity is similar in all these positions (23), this will imply a reduced IC in the lateral and upright positions. Indeed, in the present study, inspiratory capacity was 20% less in the lateral position than in the supine. Because IC can be regarded as a measure of compliance—it represents the volume change between 30 and 0 cm H_2O—it is reasonable that Crs should also be reduced.

In conclusion, we found that C_{lung}, Crs, and IC increased with growth in a regular fashion and that the two latter measures, but not C_{lung}, differed importantly between the supine and lateral positions. Likewise, there was a substantial difference in the shape of the Pes-V curve between the two body positions.

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IV

Airway closure in anesthetized infants and children. Influence of inspiratory pressures and volumes

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Abbreviated title: Airway closure in children

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Abstract

Background. Cyclic opening and closure of lung units during tidal breathing may be an important cause of iatrogenic lung injury. We hypothesized that airway closure is uncommon in children with healthy lungs when inspiratory pressures are kept low, but may occur paradoxically when inspiratory pressures are increased.

Methods. Elastic equilibrium volume (EEV) and closing capacity (CC) were measured with a tracer gas (SF_6) technique in 11 anesthetized, muscle-relaxed, endotracheally intubated and artificially ventilated healthy children, 0.6-13 years of age. Airway closing was studied in a randomized order at two inflation pressures, +20 or +30 cmH_2O, and CC and CC/EEV were calculated from the plots obtained when the lungs were exsufflated to – 20 cmH_2O. (CC/EEV > 1 indicates that airway closure might occur during tidal breathing). Furthermore, a measure of uneven ventilation, multiple breath alveolar mixing efficiency (MBAME) was obtained.

Results. Airway closure within the tidal volume (CC/EEV > 1) was observed in 4 and 8 children (not significant (ns)) after 20 and 30 cmH_2O inflation, respectively. However, CC_{30}/EEV was > CC_{20}/EEV in all children (P?0.001). MBAME was 75 ? 7% (normal) and did not correlate with CC/EEV.

Conclusion. Airway closure within tidal volumes may occur in artificially ventilated healthy children during ventilation with low inspiratory pressure. However, the risk of airway closure and thus opening within the tidal volume increases when the inspiratory pressures are increased.

Key words: airway closure; sulfur hexafluoride; anesthesia; pediatric; multibreath washout; functional residual capacity.

It has been suggested that children undergoing surgery during general anesthesia may benefit from ventilation with high inspiratory pressures and large tidal volumes because this will reduce the incidence of atelectasis (1, 2). On the other hand, this kind of ventilation may increase the risk of volu- and barotrauma (3, 4). High inspiratory pressure and large tidal volumes may thus produce cyclic opening and closing of unstable lung units which may be an important mechanism of iatrogenic lung injury in patients with adult respiratory distress disease (ARDS) ventilated with large tidal volumes (5). However, whether airway closure occurs in children below six years of age has not been studied and it is not known whether high inspiratory pressures would increase the tendency towards airway closing in children with normal lungs.

It is well known that lung collapse occurs within minutes after induction of general anesthesia in both children and adults due predominantly to a cranial shift of the diaphragam and breathing of high inspired oxygen concentration (6-9). Some of this collapse can be regained or counteracted by lung recruitment, by using low inspired oxygen concentration, and by employing positive end-expiratory airway pressure (PEEP) (10, 11, 7). Nevertheless, anesthesia makes the lungs prone to collapse, particularly in infants and children (7).

Low inspiratory pressures may not open up collapsed lung units (12), but if the inspiratory pressure is high enough to open atelectatic airways it is likely that these unstable units will also collapse during the subsequent expiration.

We thus hypothesize that ventilation with a high inspiratory pressure and large tidal volumes produces cyclic opening and closing of unstable lung units.

To test this hypothesis we studied airway closure at two inspiratory pressure levels in healthy anesthetized children. We chose to use pressure levels (20 cmH_2O and 30 cmH_2O) that would generally be viewed as “normal” and “high” inspiratory pressures in normal healthy children during artificial ventilation.

Patients and methods

Eleven children, 7 girls and 4 boys, 0.6 – 12.8 years of age, scheduled for elective surgical procedures requiring general anesthesia and endotracheal intubation, were studied (table 1).

Table 1

Demographic data

Pt. no	Age, year	Weight, kg	Height, cm	Sex	Reason for Surgery
1	0.6	8.6	67	F	Ureter inplantation
2	0.6	7.8	66	F	Partial nephrectomy
3	1.0	7.6	74	M	Colon reconnection
4	2.0	11.5	78	F	Anal atresia
5	2.6	14	92	F	Ureter inplantation
6	3.4	15.5	94.5	F	Anal atresia
7	3.8	18	103	M	Meatotomi
8	4.3	19	119	F	Ureter inplantation
9	9.8	28	134	M	Pelvis plastic of kidney
10	10.7	46	145	M	Kidney stone
11	12.8	38	155	F	Ureter stone
Mean	4.7	19.5	102.5		
SD	4.4	12.8	31.6		

Except for the problem requiring surgery, the children were healthy and had no signs of respiratory disease. The study was approved by the Human Studies Committee and parental consent was given in each case.

Procedure

Anesthesia was induced with i.v. thiopental and the patients were paralyzed with a non-depolarizing muscle relaxant (vecuronium 0.1 $mg \cdot kg^{-1}$), intubated with a cuffed endotracheal tube, and ventilated mechanically with 1% halothane in oxygen/nitrogen ($FiO_2 = 0.6$). During mechanical ventilation the ventilator (Servo 900 C, Siemens-Elema, Solna, Sweden) was set at a rate of 20-30/min, 25% inspiration, 10% end-inspiratory pause, 65% expiration, and ventilation was adjusted to give an end-tidal PCO_2 of 4-5 kPa. EKG, blood pressure, and pulse oxymetry saturation (SpO_2) were monitored in all patients.

The measurements of EEV and CC lasted 15-30 minutes and were made with the patient supine and during continued muscle paralysis. Before the measurement, i.e. 10 to 15 minutes after induction of anesthesia, the cuff of the endotracheal tube was inflated and it was ascertained by auscultation and by comparing inspired and expired tidal volumes that no leakage was present (see below). To allow normalization of CC data to absolute volumes, the CC measurements were preceded by EEV measurements.

To standardize lung volume history, the lungs were manually inflated to an airway pressure of approximately 20 cmH_2O before and after each EEV and CC determination. During EEV measurements, 5 cmH_2O of positive end-expiratory pressure (PEEP) was applied during washin (see below). To give time for the PEEP effect on lung volume to dissipate, which usually occurs within 5 breaths (13) PEEP was discontinued 0.5-2 min before starting washout (see below). Data was stored on computer discs, and flow, volume, and airway pressure were also continuously recorded on an ink-jet recorder.

Measurements

Elastic equilibrium volume was measured with an open tracer gas technique using sulfur hexafluoride (SF_6) as a tracer gas. The tracer gas concentration was measured by an infra-red analyzer placed over a cuvette in the apparatus deadspace and the flow by a heated Fleisch pneumotachograph (Gould 00, 0 or 1) with a differential pressure transducer (Validyne, MP 45-1-871). The method has been described in detail elsewhere (14-16): SF_6 is washed in through a dispensing device, which mixes SF_6 in proportion to instantaneous inspiratory flow. In this way, a uniform inspired concentration is achieved even with non-constant inspiratory flow. Washin continues until a stable end-tidal concentration of approximately 0.5% is attained. SF_6 washout is started by stopping tracer gas delivery between two inspirations, and is considered complete when mean expired concentration is less than 0.001%. Signals representing flow and SF_6 concentration are fed into a personal computer which integrates the flow signal and gives an on-line display of inspired and expired volumes and of tracer gas concentration in each breath. At the end of washout, EEV is calculated as the volume of SF_6 washed out divided by the alveolar concentration at the end of the washin period. The value is converted to BTPS conditions and apparatus deadspace is subtracted. Tidal volume, mean expired SF_6 concentration, end-tidal SF_6 concentration, and the SF_6 volume obtained in each expiration are stored on computer diskettes for later analysis of the washout curve (see below).

In the present study, apparatus deadspace was 8 ml with Fleisch pneumotachograph no. 00, 12 ml with a no. 0, and 48 ml with a no. 1. To ascertain that the lung volume was measured at zero alveolar pressure the expiration between washin and washout was prolonged to 3-5 s.

Closing was measured with the set-up shown in Fig. 1.

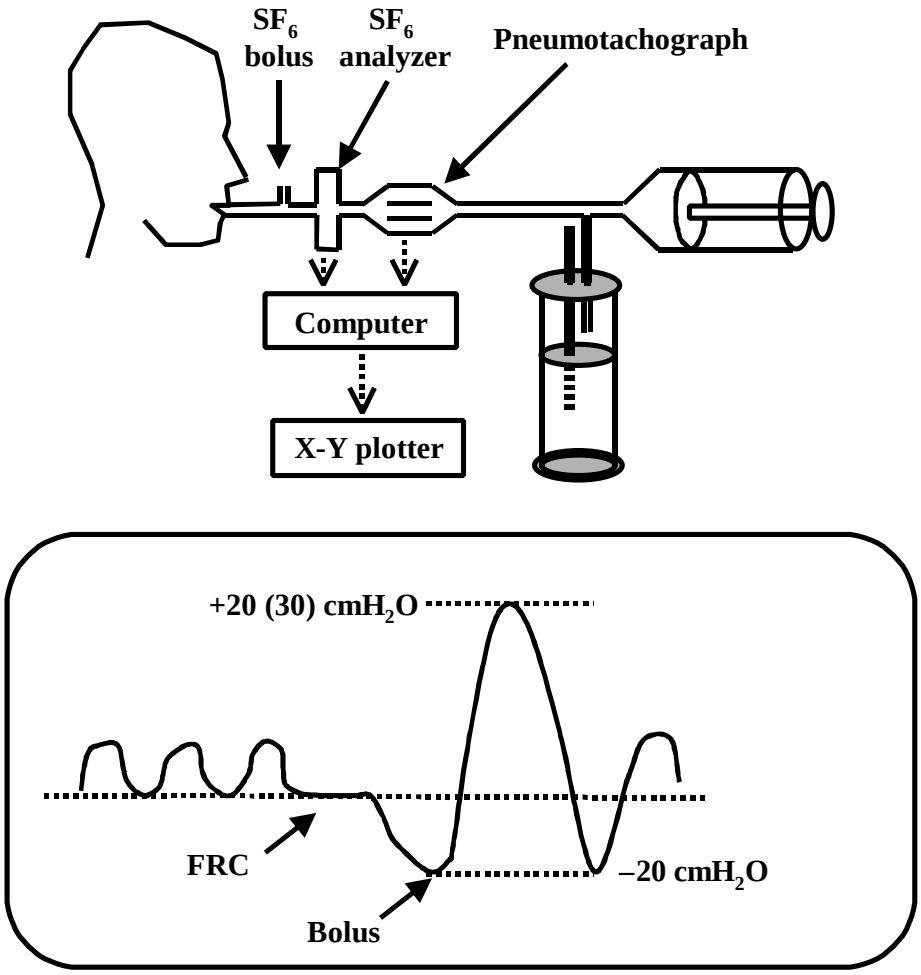

Fig. 1. The system used for closing volume measurements. During inflation the pressure was controlled by a water manometer. The volume changes during the measurement procedure are shown in the insert. The dashed arrows indicate flow of information. The apparatus deadspace between the tracheal tube and the tracer gas analyzer was 5 ml.

The flow and SF_6 signals were obtained as in the previous set-up but the child was disconnected from the ventilator and connected to a 3-litre syringe containing equal parts of oxygen and air. The measurements were done as follows: From EEV the lungs were deflated to a pressure of –20 cmH_2O, as assessed by a water manometer, a level considered to reflect residual volume (RV), a bolus of 100% SF_6 (0.005 ml/ml EEV) was administered with a

small syringe in the airway close to the tracheal tube, and the lungs were inflated to +20 cmH_2O and +30 cmH_2O. The order of inflation pressures was randomized. The volumes were registered by the computer. During the subsequent deflation to –20 cmH_2O, which was done slowly (the flow rate was 30 $ml \cdot s^{-1}$ for the youngest and 150 $ml \cdot s^{-1}$ for the oldest children) over 7-9 s to avoid dynamic compression of airways, signals representing expired tracer gas concentration and expired volume were processed by the computer and subsequently plotted on an X-Y recorder.

Calibrations

The SF_6 analyzer was calibrated with a mixture containing 0.50±0.01% SF_6 (Alfax, Sweden). The linearity of the SF_6 reading was assessed by exposing the measurement system to SF_6 mixtures of known composition, prepared by a precision gas mixer (Digamix G 18, H Wösthoff, Bochum, West Germany). The flow signal was calibrated before each measurement sequence with an accurate reciprocal pump using equal parts of air and oxygen. Zero adjustment of the flow signal was carried out before each individual measurement and the adjustment was repeated if the zero level had changed by more than 1 ml/s. A factor of 1.09 was used to convert volumes and flow from ATPS to BTPS conditions.

Data analysis

At the end of the study, copies of the expiratory curves (Fig. 2) were placed in random order and analyzed by two independent observers.

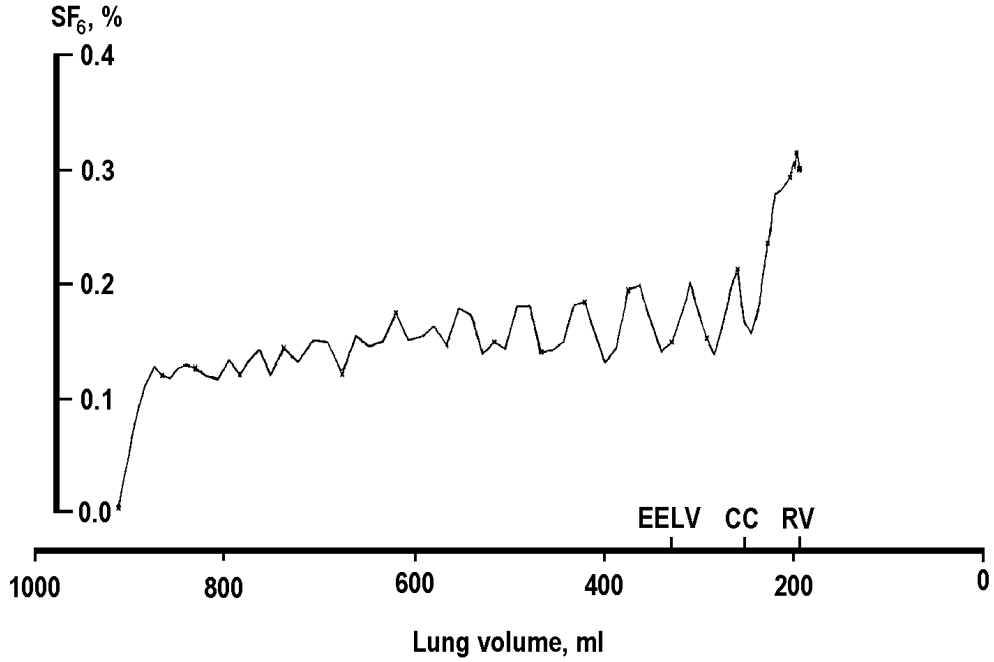

Fig. 2. Single-breath tracing obtained in a patient (2.6 years) after inflation to 30 cmH_2O. The X-axis of the original tracing has been modified to show absolute lung volumes. The position of end-expiratory relaxation lung volume (EEV) during expiration was identified by volume corresponding to the inspiratory capacity found during inspiration. Note the cardiac oscillations. The dots in the tracing are 0.4 s apart.

The closing point was taken to be the point at which upward departure occurred from a "best –fit" line through the latter half of phase III (17, 18). The volume above closing point (VaCP) was noted. Corrections were made for the apparatus and airway deadspace and the SF_6 bolus. The deadspace volume was obtained from the first washout breaths during EEV measurements as the volume expired when the SF_6 concentration had reached 50% of the tracer gas concentration at the end of phase III (19). When calculating closing capacity (CC), the deadspace value was corrected for the difference in apparatus deadspace during EEV and closing measurements. No correction was made for the effect of viscosity changes on pneumotachograph readings during the deflation-inflation maneuver – the gas mixture was nearly the same in the syringe and the lungs and the resulting error in CC values was estimated to be less than 1%.

ERV was found as the volume between EEV and ?20 cmH_2O. The vital capacity between ? 20 cmH_2O and + 20 (30) cmH_2O (VC_{20} and VC_{30}) was registered during both insufflation and exsufflation and compared.

The volume above EEV, i.e. the inspiratory capacity (IC), was defined as VC_{20} and VC_{30} minus ERV.

On the plotted curve, EEV was defined as the lung volume where the volume corresponding to IC had been exsufflated (Fig 1) and CC was found as: IC_{20} or IC_{30} + EEV ? VaCP.

To test whether the occurrence of airway closure could be predicted from other data, the slope of phase III, expressed as change in tracer gas concentration (? SF_6%) per liter during deflation divided by mean SF_6% during phase III (? SF_6%/mean SF_6%) (20, 21) and an index of ventilation inhomogeneity, MBAME, were also calculated. MBAME is defined as 100 x TO_{ideal}/TO_{actual}, where TO_{ideal} is the ideal number of turnovers (cumulative expired volume/EEV) needed to wash 90% of EEV free of tracer gas, and TO_{actual} is the actual number of volume turnovers (22). In the calculations of MBAME, volume turnovers were corrected for deadspace (19). In a previous study in supine awake, adults without lung disease, 36 ± 11 years of age, mean MBAME (± SD) was 67 ± 7%. In these patients, mean MBAME was the same during subsequent anesthesia and mechanical ventilation (19). The normal MBAME values reported from nitrogen washout are 75 ± 7% (22).

Statistics

The mean results obtained in each individual and for each inflation pressure were used for statistical analysis. Regression lines were calculated by the method of least squares. Significance of linear correlations was assessed with the t-test. The t-test for paired data was used to compare duplicate measurements and difference between inspiratory and expiratory VC. A Wilcoxon signed rank test was used to assess the effect on lung volumes and closing data when increasing the inflation pressure from 20 to 30 cmH_2O. Reproducibility is expressed as the coefficient of variation, i.e., as SD/m (=D/(m⁇2), where D is the absolute value of the difference between two observations and m the mean. The difference in number of children with CC/EEV > 1 between the two pressure levels was assessed with Fisher's exact test.

P values less than 0.05 were considered statistically significant. Data are presented as mean ± SD when not otherwise indicated.

Results

Lung volume measurements (Table II and III)

EEV was 20.2 ml/kg and inspiratory VC_{20} and VC_{30} was 29 ± 10 and 43.3 ± 12.8 ml/kg, respectively.

The coefficient of variation for duplicate measurements was 3.0 ± 2.4% (n=9, ns) for EEV and 3.3 ± 2.6% and 4.2 ± 3.7% respectively for the duplicate inspiratory and duplicate expiratory VC measurements (n=16, ns).

The inspiratory VC_{20} (n=18) and VC_{30} (n=20) was 30.4 ± 35.8 (6.0 ± 4.5%, p?0.001) and 29.3 ± 38.6 (3.7 ± 4.4%, p?0.01) ml greater, than the corresponding expiratory VC measurements.

These volume differences were thus similar and not significantly different. However, when relating the difference to age a significant connection was found: VC_{20-30}diff (ml) = 6.6 ? age (years) ? 1.9, r = 0.75, p?0.008.

Table 2

Elastic equilibrium volume (EEV) and multiple breath alveolar mixing efficiency (MBAME)

Pt. no	EELV, ml	MBAME, %
1	102	76
2	102	63
3	148	69
4	129	76
5	330	72
6	297	85
7	404	78
8	623	63
9	676	79
10	760	82
11	1559	79
Mean	466.4	74.6
SD	433.6	7.2

Table 3

Comparison of values obtained using two different inspiratory pressures

	Inflation pressure 20 cmH_2O				Inflation pressure 30 cmH_2O			
Pt. no	VC_{in}	VC_{out}	CC/EEV	Slope phase III	VC_{in}	VC_{out}	CC/EEV	Slope phase III
1	139	122	< RV	0.28	215	199	1.31	0.33
2	142	136	1.19	0.24	232	219	1.29	0.47
3	181	168	1.02	0.06	284	274	1.04	0.12
4	188	172	0.93	0.07	284	259	0.96	0.30
5	429	431	0.78	0.09	741	745	0.83	0.32
6	460	449	0.90	0.03	699	701	1.05	0.08
7	584	580	0.96	0.11	869	884	1.07	0.30
8	750	693	1.05	0.10	1169	1115	1.14	0.37
9	1070	950	0.99	0.09	1585	1464	1.03	0.32
10	1156	1122	1.05	0.02	1876	1835	1.23	0.26
11	1789	1701	0.86	0.03	2489	2398	0.96	0.17
Mean	614.0	583.2	0.95	0.10	949.4	917.4	1.06	0.28
SD	553.7	523.9	0.11	0.08	757.1	728.2	0.14	0.11

VC: vital capacity; CC: closing capacity; EEV: elastic equilibrium volume; RV: residual volume.

Closing measurements

Mean tracer gas concentration during phase III was 0.26 ± 0.09%. A phase IV phenomenon was observed in 10 of 11 children at an inflation pressure of 20 cmH_2O (i.e. one child had closing below RV) and in all 11 children at an inflation pressure of 30 cmH_2O. The coefficient of variation for VaCP values calculated from the two independent interpreters assessment of closing point was 2.4 ± 2.1% (n=36, ns). Closing capacity increased by 9.2 ± 5.3% when the inflation pressure was increased from 20 to 30 cmH_2O (p?0.005).

The CC/EEV ratio was over 1.0 in 4 children of 11 at an inflation pressure of 20 cmH_20 and in 8 of 11 at an inflation pressure of 30 cmH_2O (ns) (Fig. 3) and the ratio had no significant correlation to age, weight, or height (Fig. 3).

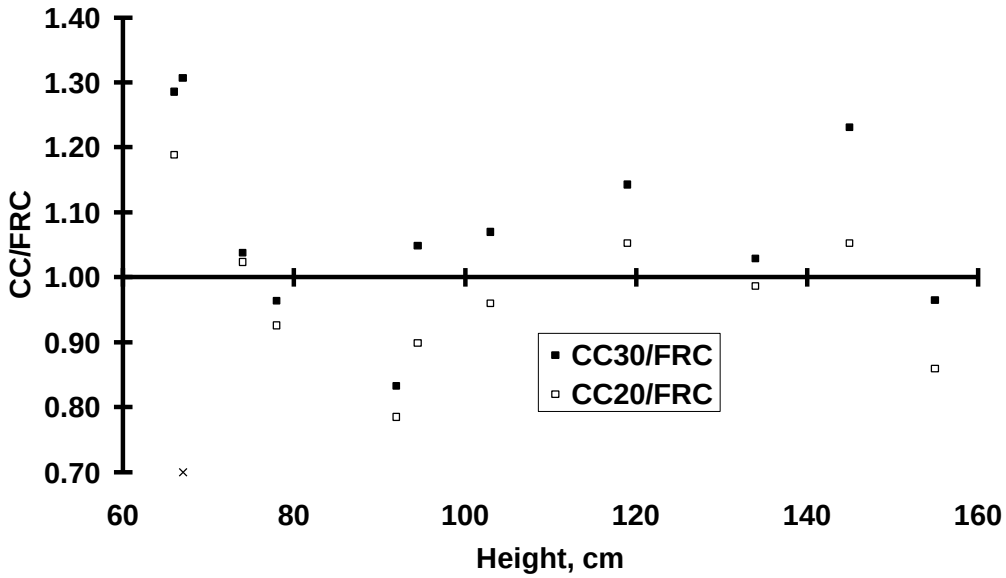

Fig. 3. The CC/EEV ratio. The ratio was higher than 1.0 in 4 of 11 children when the inflation pressure was 20 cmH_2O, and in 8 of 11 when the inflation pressure was 30 cmH_2O. One patient who did not have closing over residual volume is marked by the symbol (X).

In the 10 children in whom both inflation pressures gave closing above RV, CC/EEV obtained at an inflation pressure of 20 cmH_2O was significantly correlated to CC/EEV obtained at an inflation pressure of 30 cmH_2O (r=0.92, p?0.005) (Fig.4).

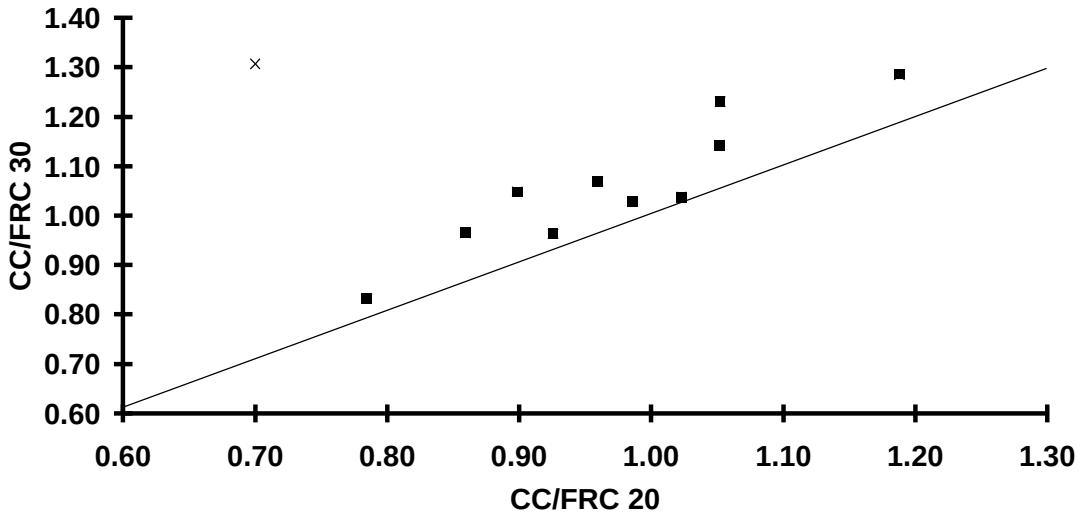

Fig. 4. The CC/EEV ratios with the inflation pressures of 20 and 30 cmH_2O were significantly correlated. One patient who did not have closing over residual volume is marked by the symbol (X). Line of identity is shown.

The coefficient of variance for duplicate measurements of MBAME was 5.2 ± 5.3% (n=11, ns). MBAME was not correlated to age, CC/EEV ratios or the difference between inspiratory and expiratory vital capacity.

The slope of phase III became steeper when the inflation pressure was increased from 20 to 30 cmH_2O (?0.003). No correlation was found between the slope of phase III and CC/EEV or MBAME.

Discussion

This study shows that: 1) Airway closure within tidal volumes occurs in healthy children during artifical ventilation at peak inspiratory pressures of 20 cmH_2O. 2) The risk of airway closure and thus also of opening and closing within the tidal volume increases when the inspiratory pressure is increased. Before discussing these findings and their clinical implications some methodological issues need to be addressed.

The method for EEV measurement used in our study has been used in studies in neonates, children, and adults (14-16). The measurements agree well with actual volumes in lung models and with body plethysmography and nitrogen washout measurements in adults (15, 14). The reproducibility in the present study is similar to our findings in earlier studies.

It should be noted that although the accuracy of EEV measurements is not unimportant when calculating the CC/EELV ratio, it has no effect on whether CC/EELV is greater than 1 or not, because this is determined by the difference between inspiratory VC and ERV measurements and the identification of the closing point (CP). The tracer gas bolus technique has been used by several earlier investigations in anesthetized patients (23, 24).

In our patients, the SF_6 bolus produced an obvious phase IV phenomenon during 21 of the 22 measurements. The identification of CP was less obvious in some patients but the agreement in measurements between the two independent observers suggests that this was not an important source of error.

Nevertheless our technique has several limitations. First, tracer gas washout techniques cannot detect firmly collapsed or consolidated lung regions. Second, the estimation of airway closure was done under quasi-dynamic conditions and not under normal tidal breathing. Although these conditions differ, it seems unlikely that airway closure would occur during tidal breathing if it cannot be demonstrated with our technique.

On the other hand, if the method indicates closing above EEV, it may very well exist during tidal breathing. We also assumed that there is equilibrium between opening and closing during tidal breathing. Thus if the method found airway closing above EEV we assumed that airway opening also occurred above EEV.

The study was designed to compare two insufflation pressure-levels; 20 cmH_2O and 30 cmH_2O. However, these pressures generated large volumes, at 20 cmH_2O a mean volume of 20 ml/kg and at 30 cmH_2O a mean volume of 36 ml/kg. Thus, even 20 cmH_2O in this setting gave a volume almost twice the size of a large normal tidal volume. This was probably due to the fact that the children had healthy lungs with high compliance and to the long duration

of the insufflation, about 2-3 s, which is two-six times the normal inspiratory time. However, it is important to realize that it is not the tidal volume in itself that opens up collapsed or closed lung units: it is the trans-pulmonary pressure in the terminal airways near the collapsed lung unit. Theoretically, a trans-pulmonary pressure of about 16 cmH_2O is needed to open atelectatic lung regions (25) and to open up all atelectatic regions induced by anesthesia in adults a mean airway pressure of 40 cmH_2O is required (12).

It is well recognized that rapid exsufflation may result in dynamic compression and gas trapping. To avoid this, we exsufflated the lungs over 7-9 s, which gave a flow rate of 30 $ml·s^{-1}$ for the youngest and of 150 $ml·s^{-1}$ for the oldest patients, well below the flow rate recommended for single-breath closing tests in children (400 $ml·s^{-1}$) (18). Still, we believe that some air trapping did occur during the exsufflation and that this is the main reason why insufflated volume was somewhat larger than the exsufflated volume during the closing maneuver. Thus, we do not think that this was due to gas exchange and oxygen consumption during this short maneuver, but more likely to airway closure with entrapment of air distal to the closed airways.

The mechanism for this may be as follows: Before the closing maneuver the patient was disconnected from the ventilator and connected to the closing volume measurement system. The 5 cmH_2O of PEEP was thus discontinued and the lungs therefore slowly emptied to EEV. In some patients this may have resulted in airway closure without air entrapment. When the lungs where subsequently inflated to 20 or 30 cmH_2O airway pressure, the closed airways opened, but during the subsequent exsufflation airways closed more rapidly and air was entrapped, resulting in a somewhat smaller expiratory VC. This interpretation agrees with the findings of Sigurdsson *et al.* (26), who observed by analyzing pressure-volume curves that the lungs lost more volume when 5 cmH_2O of PEEP was discontinued (over 6 s) in anesthetized patients with normal lungs, than could be expected on the basis of the reduction in PEEP. At 5 cmH_2O the lost lung volume was about 160 ml. Most of the lung volume was regained when the airway pressure was again increased above 20 cmH_2O. If this explanation were correct, one would in our study expect CC to decrease by about 30 ml with decreasing exsufflation rate.

We found that the CC/EEV ratio was > 1 in four of the 11 children when the insufflation pressure was 20 cmH_2O. This indicates that airway closing might occur during tidal breathing when end-inspiratory airway pressure is 20 cmH_2O. However, our measurement was performed during quasi-dynamic conditions. Furthermore, EEV was estimated from the

starting point of the maneuver. Since we found the exsufflated air was about 30 ml, i.e. 4-6% less than the insufflated air, we can presume that this air was trapped in the residual volume and that the "dynamic elastic equilibrium volume" could have been located at a higher level than we estimated. This fact is important since in the four children that had a CC/EEV > 1 with the closing maneuver performed at 20 cmH_2O, CC/EEV was very near 1, indicating that a small under-estimation of the location of elastic equilibrium volume would indeed change the ratio to below 1. Moreover, as mentioned, 20 cmH_2O insufflation gave a volume almost twice a normal large tidal volume. If instead we had adjusted the insufflation pressure to obtain a 10-15 ml/kg inspired volume, which is similar to a normal tidal volume, the insufflation pressure would have been lower. A lower airway pressure would open up fewer, if any, closed units and we would probably have found few, if any, signs of closing above EEV. As also discussed, the finding that most children had no airway closure above EEV does not exclude the possibility that the children had atelectatic lung regions. Our results only indicate that these regions did not open and close when 20 cmH_2O of airway pressure was applied and withdrawn, suggesting that this it not likely to occur during tidal breathing using the same inspiratory pressure. Hence, from our data we can deduce that airway closing and opening might occur, but are probably not common during artificial ventilation at low inspiratory airway pressures. This is also supported by the fact that we did not find any correlation between MBAME and CC/EEV. Closing of airways within tidal breathing would theoretically give a low MBAME.

The ratio CC/EEV did increase when the insufflation pressure was increased to 30 cmH_2O. This agrees with findings by Holz *et al.* in awake adults (27) and Hedenstierna in anesthetized adults (28). Very interestingly, in our study the difference between insufflated and exsufflated volume was numerically the same at an insufflation pressure of 30 cmH_2O as at 20 cmH_2O. This implies that increased closing tendency was not due to closure of small airways with increased trapping of air, since this would have increased the difference between insufflated and exsufflated air. Instead, we believe that the cause was the opening of collapsed unstable lung units during insufflation, which then again closed totally above EEV during exsufflation. Hence, high inspiratory pressures might cause cyclic opening of collapsed lung units with subsequent closing. Repeated opening and closing of lung units generates extremely high shear forces in the lung parenchyma (29). A method to avoid cyclic opening and closing of lung units in collapse-prone lungs is to apply a high and sustained airway pressure in order to recruit collapsed lung regions before starting ventilation and then to use PEEP to avoid collapse of the regained lung volume (30, 31). This method has been

found to improve survival in patients with acute respiratory distress syndrome (ARDS) and is also associated with decreased pro-inflammatory systemic release of cytokines and lower incidence of multiple organ failure (32-34). Another method is ventilation with small tidal volumes. Indeed, the ARDS-network study showed that small tidal volume ventilation improved survival in patients with respiratory distress (35). Small tidal volumes would probably not generate a pressure high enough to open up collapsed lung. According to the reasoning above, this would decrease the tendency of cyclic opening and closing of lung regions. In addition, ventilation with small tidal volumes would decrease the risk for overdistension. In numerous animal experiments large tidal volume ventilation and high inspiratory pressures have been found to cause severe lung injury (36-39). In many of these studies it has been discussed whether pressures or volumes overdistension is the more harmful. However, overdistension is caused by stretching of the membranes around the alveoli and terminal airways, and according to Laplace´s law this depends on both volume and pressure.

In adult patients with normal lungs ventilated short-term with 15 ml/kg tidal volumes Wrigge *et al.* did not find any mechanical or biochemical indication of lung injury (40). However, in their study the mean peak inspiratory pressure was only 16 cm H_2O, which supports our notion that higher pressure is needed to open up closed lung units and thus induce cyclic opening and closing of lung regions and lung injury.

In conclusion, our study indicates that opening and closing of lung units might occur, but is probably not common, at artificial ventilation at an inspiratory pressure of 20 cmH_2O of inspiratory pressure. However, when the airway pressure is increased to 30 cmH_2O it seems to be more regular and we therefore believe that also in healthy children it is pertinent to avoid such a high inspiratory pressure.

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