Clinical Applications of Infant Lung Function Testing

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The printing of this thesis was financially supported by :
GlaxoSmithKline BV, Sanquin Bloedbank Regio Zuidwest,
Nutricia Nederland BV, Roche Nederland BV, IVAX Farma BV,
Aerocine AB Sweden, Novartis Pharma BV, AstraZeneca BV,
Merck Sharp & Dohme BV, Nederlands Asthma Fonds.

ISBN: 9061095646
Printed by Alfabase, Alphen aan den Rijn (info@alfabase.nl)
Layout and cover design: studio Tjonge (www.studiotjonge.nl)
Published by Uylenburgh Pers, Amsterdam

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Klinische toepassingen van longfunctie onderzoek bij zuigelingen en peuters

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus
Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 10 juni 2004 om 13:30 uur

door
Ward Hofhuis
geboren te Rotterdam

Promotiecommissie

Promotor :	Prof.dr. J.C. de Jongste
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Inhoud

BACKGROUND OF INFANT LUNG FUNCTION TESTING

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1. Introduction

In the 1940s and 1950s pulmonary function testing in adults and older children began to develop as a science with clinical, epidemiological and research applications. However, lung function measurements in infants lagged behind for a number of reasons (1):

1. Infants are uncooperative and therefore difficult to study
2. The tests usually require the infants to be asleep; hence sedation is often required
3. Some tests are invasive
4. Disease or illness state often makes testing impractical or impossible
5. Parental and doctor concerns exist over testing and sedation
6. Lung dynamics may change rapidly
7. There is a lack of physicians, scientists and sponsors interested in this field

In the past 20-25 years there has been an increase in interest in studying the respiratory system in infants, and as a consequence, the development and application of new tests (1). Initial tests of lung function in infants focussed predominantly on measurements of dynamic compliance, resistance and lung volumes. Later, other tests have been developed, such as the forced expiratory manoeuvres by chest compression technique. The advances made in the development and application of new tests have led to a wide range of applications of respiratory function tests in infancy, as summarised in table 1. Infant lung function tests are performed in several specialised centres around the world. Recently published standards and normal values for infant lung function testing allow clinical applications of the lung function tests, accurate measurements and comparisons between centres (3-5). In this chapter different methods of lung function testing in infancy are dicussed, with the focus on the

methods used in our research. Moreover, clinical and epidemiological applications of infant lung function testing are dicussed.

1. Increase basic knowledge	• Lung growth, development and function
2. Diagnosis	• Of lung impairment
	• Of physiologic processes
3. Quantitate severity	• Predict prognosis
4. Evaluate therapy	
5. Epidemiologic evaluation	• Of natural history of disease
	• Of risk factors for subsequent disease
6. Determine risk	• Preoperative evaluation
7. Evaluation of disability	• Medical, legal and ethical issues

Table 1. Uses of Respiratory Function Tests in Infancy (1)

2. Infant Lung Function Testing

2.1 Sedation

Most Infant Lung Function Tests (ILFT) require that the infant is asleep. To facilitate sleep, tests are performed at a time of day when the infant usually sleeps. To prevent the infants from waking up during the measurements, the infants are mostly sedated with chloral hydrate (25-100 mg/kg) (6). Sedation by means of chloral hydrate carries a small risk for respiratory depression (7). Therefore, heart rate and transcutaneous oxygen saturation (SaO_2) are monitored continuously. Moreover, the infants are discharged when awake and alert, with a minimum of 2 hours after administration of the drug. This is in accordance with 'Sedation and Analgesia for Procedures in Children', where it is stated that chloral hydrate has a well-established safety profile and it is the preferred sedation for non-invasive procedures in patients less than 3 years of age (6). Nevertheless, one study showed that a dosage higher than 70 mg/kg may cause a fall in arterial oxygen saturation and a decrease in clinical score of infants recovering from acute viral bronchiolitis (7). Therefore, it was suggested that wheezy infants with baseline SaO_2 less than 95% are more susceptible to central respiratory depression following sedation with chloral hydrate (7).
When the infant is asleep several measurements of lung function can be performed, such as lung volume, forced expiratory manoeuvres, compliance, resistance and conductance. In this thesis we focus on measurements of lung

volume (2.2) and forced expiratory manoeuvres (2.3). Other measurements of lung function during infancy are summarised in chapter 2.4.

2.2 Lung volume

Measurement of lung volume

The only lung volume that can be measured reliably and routinely in infants is the resting end-expiratory lung volume, i.e. the functional residual capacity (FRC) (figure 1). It is important for interpreting volume-dependent pulmonary mechanics, such as forced expiratory flows, for defining normal lung growth (4) and for detecting hyperinflation, a measure for dyspnoea or disease state. Two techniques are commonly used to measure FRC in infants: whole-body plethysmography (FRC_p) or gas dilution spirometry, using either Helium dilution (FRC_{He}) or N_2 (FRC_{N2}) wash out. Measurement of FRC by means of plethysmography is also known as thoracic gas volume (TGV) and measures all the compressible gas within the thoracic cage, including that which is not in direct communication with the airway opening. Therefore, consistently higher values for FRC of approximately 15% have been obtained by plethysmography in healthy infants and young children, as compared with gas dilution techniques (8-11). This may reflect some degree of airway closure during tidal breathing and/or poor gas mixing in infants in young children (12). We chose plethysmographic measurement of FRC, since it is simple to apply and, unlike the gas dilution techniques, enables repeated measurements of lung volume to be obtained within a few minutes (4).

Measurement of FRC by plethysmography (FRC_p) is based on Boyle's law. Boyle's law states that when a gas in a closed container is compressed under isothermal conditions, its volume decreases as the pressure inside the container increases such that the product of volume and pressure at any given moment is constant. Hence, $P \cdot V = \text{constant}$, or $P_1 \cdot V_1 = P_2 \cdot V_2$, where the subscripts 1 and 2 indicate the original and altered conditions of the gas, respectively (12).

Explained in a simplified way: The volume and pressure within the box are known. The box-volume (V_1) is the empty box-volume minus the volume of the infant, which can be calculated from the infant's weight and length. The pressure within the box (P_1) is measured. At end-expiration, the volume in the lungs (V_2) is the FRC, and the pressure within the alveoli (P_2) equals to box pressure

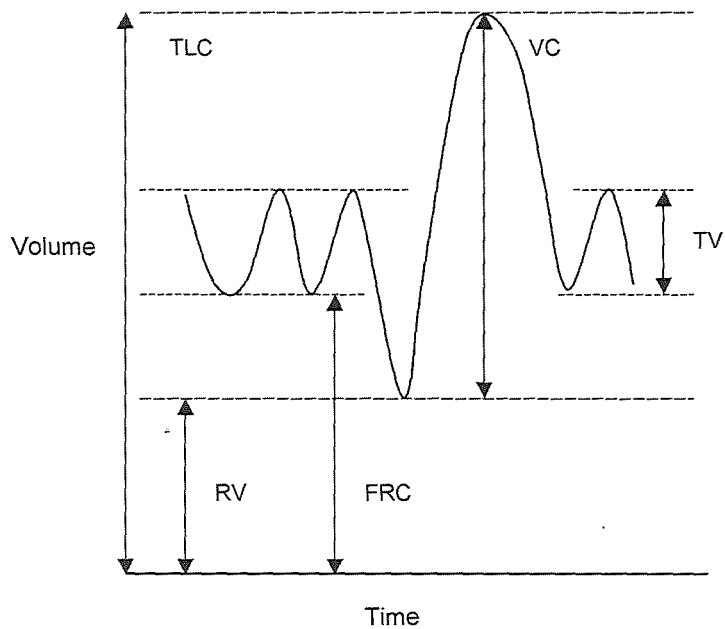

Figure 1. Schematic spirogram. FRC: functional residual capacity. RV: residual volume. TV: tidal volume. TLC: total lung capacity. VC: vital capacity.

(P_I). Following an inspiratory effort against the closed shutter (Figure 2), there will be a decrease in alveolar pressure and a corresponding increase in lung volume. In the box there will be a corresponding increase in pressure and decrease in volume. Vice versa, following an expiratory effort against the closed shutter, there will be an increase in alveolar pressure and a corresponding decrease in lung volume. In the box there will be a corresponding decrease in pressure and increase in volume. The volume shifts within the box, and the pressure shifts within the box and within the alveoli are known (pressuming the pressure at the mouth is the pressure within the alveoli). During these respiratory efforts, $P_1 \cdot V_1 = P_2 \cdot V_2$, meaning there is an equation with 4 variables of which 3 are known. Hence, the lung volume (V_2) can be calculated. In practice, the actual volume measured includes the apparatus dead space and any tidal volume inspired above end-expiratory level at the moment of occlusion. These must be subtracted from the measured volume to obtain the FRC (12). A detailed description of the FRC_p calculation can be found in: Stocks et al. Infant Respiratory Function Testing; John Wiley-Liss & Sons, Inc., New York (12).

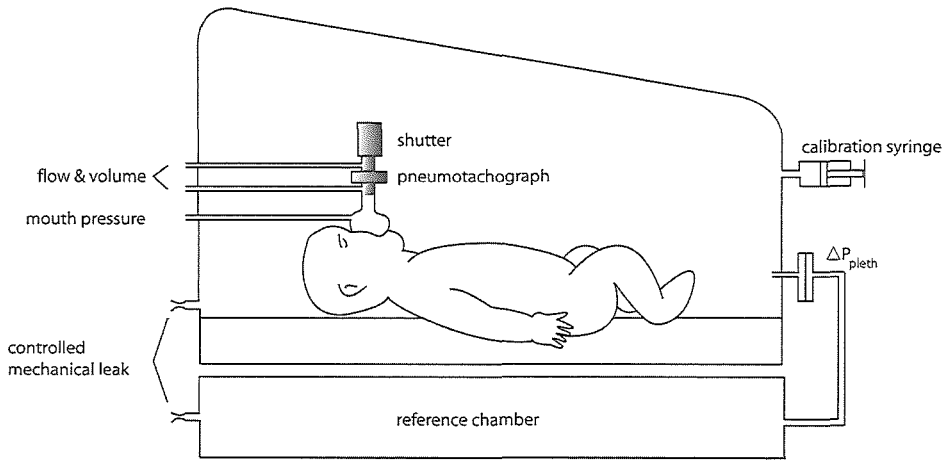

Figure 2. Schematic diagram of an infant whole-body pressure plethysmograph for measuring functional residual capacity (FRC). The figure is modified from Stocks et al. Plethysmographic assessment of functional residual capacity and airway resistance. 1996 (12).

Assumptions and limitations

Measurement of FRC_p is based on a number of assumptions (12):

- There is no flow of gas in the airway during the occlusion

Flow in the airway may occur during occlusion in the presence of non-uniform alveolar pressures (13). It is suggested that equilibration of the pressures in the airways and at the airway opnening can be improved by performing airway occlusions at higher lung volumes (i.e. at end-inspiration) when the airways are more distended (with a lower resistance and hence shorter time constant), and correcting the measured volume for inspired tidal volume (4, 12, 14). Advantages of occluding at end-inspiratory level are that glottic closure is less likely to occur than during end-expiratory occlusions (12), and that the infants are less likely to wake up from the measurement (own observations). However, the question of the optimal point of occlusion with respect to providing the most accurate results in wheezy babies is not clear (12).

- Pressure changes applied to the lung are homogeneous within the pleural space

In infants with respiratory disease, there may be a non-uniform distribution of ventilation. As a consequence, the pressure differences at the airway opening

may not reflect the pressure differences in the alveoli, resulting in an over- or an underestimation of FRC_p (12, 15).

• Pressure-volume changes are limited to the volume of gas within the thorax
Measuring lung volume by means of a plethysmograph has as a disadvantage that also part of the volume of gas within the abdomen is measured. The effect depends on the relative amount of compressable gas in the gastrointestinal tract. Under normal circumstances, it may be assumed that the volume of gas in the gastrointestinal tract is either insignificant or not compressed, since changes in the intra-abdominal pressure are relatively small compared to changes in pressure at the airway opening during airway occlusions (12, 15, 16).

• Changes in pressure and volume are isothermal
When a gas is being compressed heat is gained because the average energy of the molecules increases. Isothermal conditions imply that, during either compression or expanding of the gas, heat is exchanged so rapidly across the walls of the container that gas temperature remains the same. The proximity of gas to tissue within the respiratory system is such that any heat generated during occluded respiratory manoeuvres is rapidly absorbed, so that changes of alveolar volume will occur under isothermal conditions, even at high frequencies (12).

Data collection
When measuring FRC_p there are several points to consider (4). The most important ones are that there should not be any face-mask leaks, occlusion should preferably be at end-inspiration and after releasing occlusion check for post-occlusion end-expiratory level, to detect possible face-mask leaks.

Reporting results
The mean ± standard deviation of 3 to 5 technically satisfactory FRC_p measurements should be reported. This can be done in absolute values (mL), or in mL per kilogram bodyweight (mL/kg). FRC_p can also be reported in relation to the predicted value: Z score, also known as standard deviation score.
The (preliminary) equation used for predicting FRC_p in healthy infants up to 15 months is:
FRC_p (mL) = $2.36L^{0.75} \times W^{0.63}$ (RSD = 0.140),
where L is crown heel length (cm) and W is bodyweight (kg) (4).
The equation used for calculating FRC_p in Z score is (4):
(LN (measured value FRC_p) – LN (predicted value FRC_p)) / 0.140
or

FRC_p in Z score = (LN(FRC_p) - LN(2.36) – 0.75 LN(L) – 0.63 LN(W)) / 0.140

Recently, new low deadspace equipment for plethysmographic measurements of FRC has been developed (Jaeger Masterscreen BabyBody Plethysmograph, VIASYS Healthcare, Germany). Healthy infants measured with this new equipment had a mean (SD) FRC_p in Z score of –2.3 (1.2), which was significantly lower than predicted (17). Therefore, published prediction equations should not be used to interpret FRC_p results obtained with this new low deadspace equipment. This would run the risk of missing significant hyperinflation in those with airway disease. New reference data should therefore be obtained for using this new equipment must be established (17). Since we used equipment to measure FRC according to present guidelines, on which the reference data are based (4), we believe we correctly expressed FRC_p in Z score.

2.3 Forced expiratory manoeuvres

In co-operative children and adults, forced maximal expiration is the most common and robust lung function test, for both clinical and research settings. Forced expiration produces several indices, including measurement of the total volume expired (Forced Vital Capacity (FVC)), volume expired in a given time (forced expiratory volume/time (FEV_t)), peak expiratory flow (PEF) and maximal expiratory flow at specified lung volumes (18). The FEV_1 is a useful respiratory function parameter in older children and adults, achieving good sensitivity with low variability (18). The forced vital capacity (FVC) manoeuvre involves maximal inspiration followed by a rapid and maximal forced expiration. Nowadays, the FVC manoeuvre is mainly used to assess obstructive lung disease (18). In case of flow limitation, an increase in the pressure to generate flow will not result in more flow.

There are two ways in which forced expiration can be achieved in infancy. One is to use negative pressure. This can be done via a tracheal tube. The main disadvantage of this forced deflation technique is its limitation to use in subjects who have a tracheal tube or tracheostomy cannula, and that the subjects must be deeply sedated or anesthetised. The invasive nature of this method precludes its use in the routine setting (18). More recently, Jones and coworkers (19) showed that negative expiratory pressure (NEP) at the airway opening can be used as a noninvasive technique in infants to assess flow limitation during forced expiratory maneuvers. More studies are needed to validate this technique in a clinical setting. The other way in which forced expiration can be achie-

ved is to use externally applied positive thoracoabdominal pressure. This can be done within the tidal breathing range (tidal volume forced expiration, 2.3.1) or after inflation of the lungs to a given airway pressure (raised volume forced expiration, 2.3.2).

2.3.1 Tidal volume forced expiration

Measurement of Tidal volume forced expiration

For the measurement of forced expiration during tidal breathing the rapid thoracoabdominal compression (RTC) technique is used since 1982 (20). The RTC-technique, or squeeze technique, is the first practical, non-invasive method with the ability to asses airway physiology in both healthy and diseased infants. A diagram of the experimental set-up is shown in figure 3.

A non-elastic jacket is wrapped around the infant's chest and abdomen with the arms inside or outside the jacket. The jacket contains an inflatable part that is positioned against the infant's anterior chest wall and upper abdomen. At end-tidal inspiration the jacket is inflated rapidly, resulting in a forced partial expiratory flow-volume curve. The parameter of interest is the flow at FRC. Jacket pressure is increased gradually in steps of 20 cm H_2O in repeated squeezes, resulting in an increase of the flow at FRC. At a certain point an increase in the jacket pressure does not result in a further increase of flow at FRC, i.e. the maximal flow at FRC ($V'max_{FRC}$) is obtained (Figure 4). If this optimal jacket pressure is exceeded, curve shape will become progressively more concave and $V'max_{FRC}$ will decrease. According to guidelines, this optimal pressure should then be used throughout the procedure, including after therapeutic interventions such as bronchodilator administration (3). However, therapeutic interventions are known to influence airway characteristics (21). Therefore, one might argue if one should reassess the lowest pressure at which the highest flows are obtained, irrespective of the jacket pressure used before the therapeutic intervention. Equipment and procedures should be standardised in accordance with guidelines (3).

The main differences between tidal volume forced expiration and formal spirometry in older children is that the former is limited to the tidal volume range, and that the expiration is passive. The flow-volume curve assessed by means of the RTC technique can be interpreted by evaluating the shape of the flow-volume curve and the presence of tidal flow limitation (22, 23), but the parameter

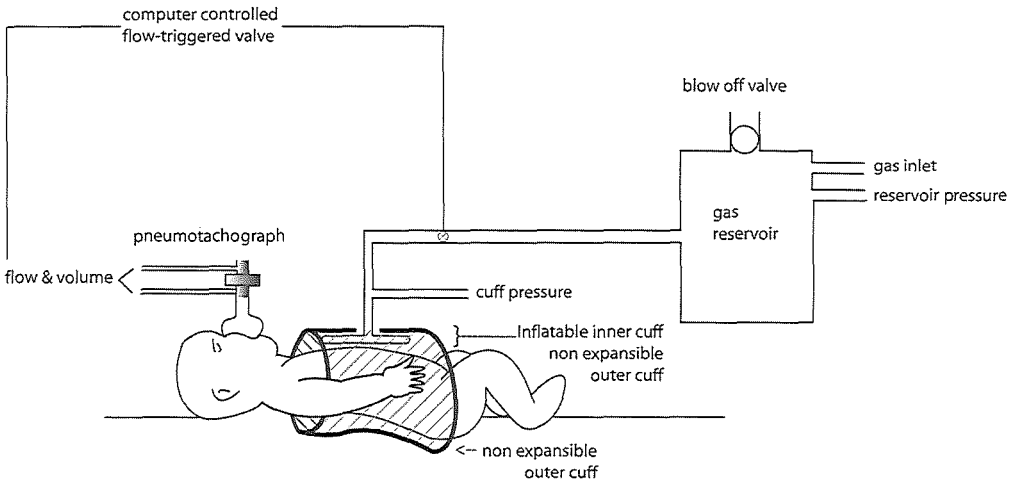

Figure 3. Schematic diagram of the experimental setup for the rapid thoracoabdominal compression (RTC) technique of measuring partial expiratory flow-volume curves. The figure is modified from Le Souëf et al. Forced Expiratory maneuvers. 1996 (18).

most used in infants is the maximal flow at FRC ($V'max_{FRC}$). $V'max_{FRC}$ is thought primarily to reflect airway mechanics upstream to the airway segment subjected to flow limitation, and therefore is a measure of peripheral airway function that is relatively independent of the upper airway resistance (20, 24). This is also shown by the negative correlation between $V'max_{FRC}$ and resistance measurements by means of the interrupter technique (R_{int}) (25). Little is known about the relation between lung function parameters measured during infancy and lung function parameters in older children. Only one study attempted to relate lung function during infancy (at 6 months of age) to lung function in childhood (at 6 years of age) in 29 patients with cystic fibrosis (26). The measurement of $V'max_{FRC}$ was obtained at a lung volume close to MEF_{50} and MEF_{25}, both of which can be used for comparison. However, when $V'max_{FRC}$ scores were compared with FVC, FEV_1, MEF_{50}, or MEF_{25}, no significant relationship was found (26).

Determinants of expiratory flow limitation

The intention of the RTC technique is to assess airway function by achieving

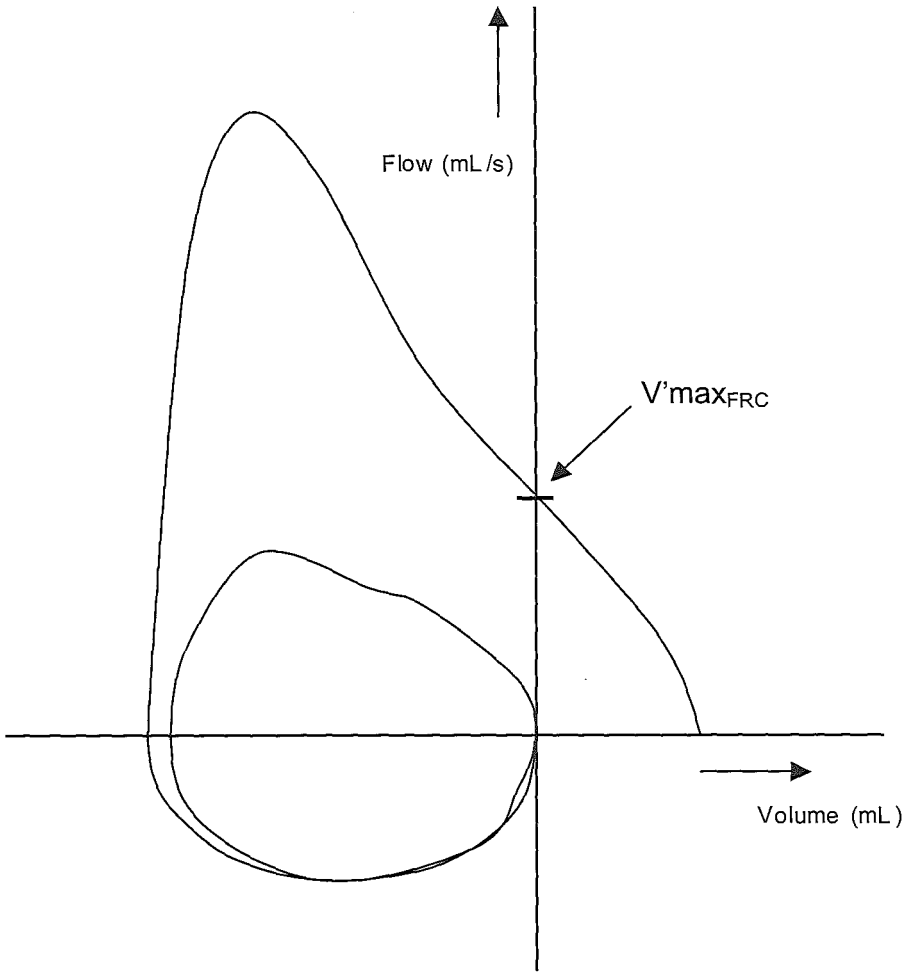

Figure 4. Flow-volume curve showing the maximal flow at functional residual capacity (V'max$_{FRC}$).

expiratory flow limitation during tidal breathing. The description of flow limitation is simple: at a given lung volume, flow is independent of the difference between alveolar pressure and mouth pressure if that pressure difference is sufficiently large (27). In older children and adults, maximum expiratory flow-volume (MEFV) curves are largely reproducible in any subject, because beyond a critical level of effort the flow is effort-independent. This strongly suggests

that within the lung there is a mechanism which limits the expiratory flow (28). Several investigators explained that airflow is limited because of compression of intrathoracic airways when intrabronchial pressure becomes lower than pleural pressure during expiration (29, 30). However, the mechanism is more difficult. The intrapulmonary airways are compliant and during a forced expiration the pressure distribution inside the bronchial tree depends on lung volume, gas properties, flow and airway calibre. Thus the mechanics of the airways and the flow are coupled (27). From work outside lung mechanics, it has been predicted that flow limitation in elastic tubes occurs at the speed at which the fluid in the tube transmits pressure waves: the tube wave speed, which is dependent on tube stiffness and the density of the gas or fluid (28). The tube wave speed multiplied by the cross-sectional area of the airway equals the wave speed flow, which equals the maximal airflow that can pass at a given location in the bronchial tree (27). Thus, the wave speed flow depends on the gas density, the compliance (i.e. stiffness) of the airway and the airway cross-sectional area. The less dense the gas, the stiffer the tube wall and/or the larger its cross-section, the higher the speed wave and hence the higher the flow that can theoretically pass the tube (27). The bronchial tree can be regarded as a series of airways each with their own wave speed flows. Flow limitation will occur at that point along the bronchial tree at which local wave speed flow is minimal for a given lung volume: this point is called the choke point. During a forced expiration many of the factors determining wave speed flow change, therefore, choke points move and jump from one generation to another. Moreover, multiple choke points may be present in parallel airways, and the expiratory airflow is the sum of wave speed-limited airflows from different airways and lung zones (27).

These studies were performed on adult subjects. It is not known if these mechanisms for flow limitation aslo apply for infants using the RTC technique, or even the raised volume RTC (RVRTC) technique. A major difference between the RVRTC technique in infants and MEFV curves, is that in the former the driving force for the forced expiration is the externally applied jacket pressure. Possibly, the airway mechanics of flow limitation may be different for the RTC technique with a more prominent role for the compression, or even collapsibility, of intrathoracic airways when intrabronchial pressure becomes lower than pleural pressure during forced expiration. Whether or not the flow limiting segment during forced expiration using the RTC technique is in the peripheral airways, is not proven. Therefore, the statement that $V'max_{FRC}$ is thought to be a measure of peripheral airway function (20, 24) remains a hypothesis.

Assumptions and limitations

Although the RTC technique is well accepted and standardised, several disadvantages have become apparent. First, measurement of $V'max_{FRC}$ relies on FRC not changing between forced expirations. There is abundant evidence that FRC is not stable and shifts with dynamic events such as changes in airway calibre (31), sleep state or addition of dead space (18, 32). This explains the high variability of $V'max_{FRC}$ for which coefficients of variation (CV) range from 11% to 36% (18). However, a recent study evaluating the reproducibility of $V'max_{FRC}$ showed that the CV for a single measurement of $V'max_{FRC}$ was as low as 6.9% (33). This number is similar to that from forced expiratory flows at late expiration in adults (33, 34). Second, flow limitation is difficult to ascertain, especially in healthy infants. Finally, RTC technique assesses airway function in the tidal volume range only, which reduces its sensitivity for obstructive abnormalities (18, 35).

DATA

Curve shape

The shape of forced expiratory flow-volume curves is of interest, because it reflects airway mechanics, although in a qualitative manner (22):

- Convex curves (curved away from the expiratory flow and volume axes) are common in normal infants (figure 5a),
- Concave curves (curved towards the expiratory flow and volume axes) are common in infants with airway disease (figure 5b),
- Tidal flow limitation, defined as no difference between tidal and forced flow during the last 50% of the forced expired volume is a sign of severe airway obstruction (figure 5c).

The compression pressure also dictates curve shape with a progressive shift from convex to concave with increasing compression pressure (36).

Pressure transmission

Measurement of efficacy of jacket pressure transmission is the percentage of pressure transmision across the chest wall from the inflatable jacket to the intrapleural space. Pressure transmission is easily measured using a noninvasive occlusion technique (3, 37, 38). In short, the airway is occluded manually at end-inspiration until the pressure trace has reached a plateau. Then the

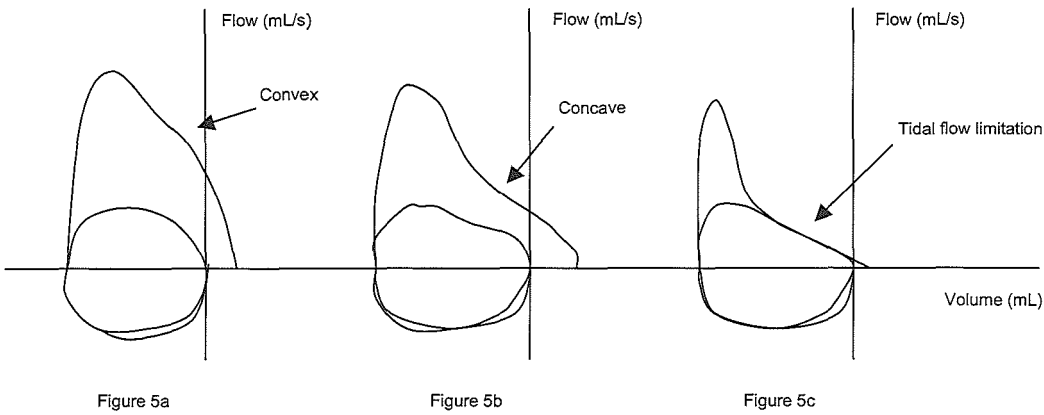

Figure 5a Figure 5b Figure 5c

Figure 5. Different shapes of forced expiratory flow-volume curves

jacket is inflated using the optimal jacket pressure and again the pressure is allowed to reach a plateau, after which the occlusion is released. The difference between the two plateaus is the pressure change within the respiratory system and represents the amount of pressure transmitted to the intrathoracic structures at end inspiration during the squeeze. Jacket efficiency can range from 20-70%, mostly depend on the thightness of the jacket, and is essential for comparing data within and between centres.

Data collection

Once the optimal jacket pressure for measuring $V'max_{FRC}$ has been obtained, 3 to 5 good quality flow-volume curves should be recorded at this compression pressure. There are several collection criteria for $V'max_{FRC}$. Important is that there is a regular breathing pattern and that inflation of the jacket is maintained throughout the entire forced expiration (3). For the flow-volume curves it is important that the peak flow has occured within the first 30% of the volume of the previous tidal breath and that the forced flow-volume curve continues past previous stable FRC (i.e. EEL). The flow-volume curve may not show evidence of early inspiratory effort or glottic closure, particularly in the last 50% of expiration (3).

Reporting results

Controversy exists as to the best way to report $V'max_{FRC}$. Although an argument can be made for reporting the single highest or maximal value (3), it is

thought more appropriate to report the mean of three to five acceptable measurements (3, 18). Although this appears to be contradictory for a 'maximal' parameter, it is rational in view of the relative high variability of $V'max_{FRC}$. Furthermore, maximal or peak expiratory flow is not useful, as it is largely determined by compression pressure (36). According to the task force for ILFT the coefficient of variation (CV) of 3 to 5 technically acceptable curves should also be reported as a measure of the intrasubject variability (3), which normally ranges from 11% to 36% (18). In addition, $V'max_{FRC}$ should be reported as the absolute value in mL/s and not merely as a percentage of the predicted value, as there is a wide range of 'normality' for $V'max_{FRC}$ (3).

However, as normal values of $V'max_{FRC}$ have been published (3, 5), $V'max_{FRC}$ can also be reported in Z score, also known as standard deviation score. A Z score of 0 ± 2 SD indicates a normal range for $V'max_{FRC}$. Appropriate use of Z scores improves interpretation of both clinical and research studies (5). Gender specific prediction equations for $V'max_{FRC}$ in infancy were published by the ILFT task force (3), and more recently by Hoo and co-workers (5):

The gender specific equations published by Sly and co-workers on behalf of the ILFT task force for infants between 0 and 32 months is (3):

- Boys: $V'max_{FRC}$ predicted (mL/s) = 114 + (3.4 x postnatal age). SD = 80.95
- Girls: $V'max_{FRC}$ predicted (mL/s) = 136 + (2.9 x postnatal age). SD = 85.44

Where the postnatal age is the age in weeks (3). In premature born infants the postnatal age should be corrected to 40 weeks gestational age. The equation used for calculating $V'max_{FRC}$ in Z score is: ($V'max_{FRC}$ measured - $V'max_{FRC}$ predicted) / SD

More recently, Hoo and co-workers published gender specific equations (5):

- Boys: $(V'max_{FRC}$ predicted$)^{0.5}$ (mL/s) = 4.22 + 0.00210 x length^2. RSD = 3.01
- Girls: $(V'max_{FRC}$ predicted$)^{0.5}$ (mL/s) = -1.23 + 0.242 x length. RSD = 2.72

Where length is in centimeters.
The equation used for calculating $V'max_{FRC}$ in Z score is:
$((V'max_{FRC}$ measured$)^{0.5} - (V'max_{FRC}$ predicted$)^{0.5})$ / RSD

As shown, the prediction equation by Sly and co-workers uses age as the independent variable, whereas the prediction equation by Hoo and co-workers uses length as the independent variable. Some infants are small for their age, due to

an underlying disease such as chronic lung disease or cystic fibrosis. If one uses the prediction equation with age as the independent variable for infants who are small for their age, one could find a lower $V'max_{FRC}$ (Z score), as compared with a $V'max_{FRC}$ (Z score) calculated using length as the independent variable. We believe that in these cases one should use the equation by Hoo and co-workers, as the use of length as an independent variable partly corrects for the presence of disease.

2.3.2. Raised Volume forced expiration

Measurement of Raised Volume Forced Expiration

In adults, assessing forced expiration over the full vital capacity range produces superior information compared to the tidal range (18). Several important aspects of such spirometric assessments have been identified. First, reproducible lung volume landmarks, such as total lung capacity (TLC) and residual volume, are available. Second, forced expiratory volume in 1 second (FEV_1) offers an excellent compromise between sensitivity and reproducibility. Finally, with modest effort, forced expiration is largely flow-limited meaning that FEV_1 is highly reproducible. In contrast, parameters from tidal volume assessments are poorly reproducible, as there are no stable lung volume landmarks and maximal expiratory flow changes with alterations in absolute lung volume (18).
Recently, the raised volume rapid thoracoabdominal compression (RVRTC) technique has been developed, in which the infant's lungs are inflated to a given airway pressure. This way, the lung volume from which the forced expiration occurs, can be standardised to a given pressure. While it can not be assumed that a given airway pressure will achieve a certain percentage of TLC, the curves produced closely resemble conventional flow-volume curves obtained from TLC, i.e. spirometry as performed by adults and schoolchildren (35). The success of raised lung volume relies largely on the Hering-Breuer inflation reflex (HBIR) (35). The HBIR is defined as a relaxation of the respiratory muscles after airway occlusion at volumes above FRC. The HBIR is volume dependent, and hence stronger and more consistently present at raised volume (39). Nowadays, raised volume assessments in non-intubated infants are made by inflating the lung to a given airway pressure using either an external gas source, or a pump (18).

Advantages and disadvantages

The raised volume forced expiration has several advantages over the RTC tech-

nique (18, 35): First, lung volume can be standardised to a given airway pressure. This means that comparisons can be made between raised volume breaths either between measurements in the same individual or between infants. Second, since the HBIR is volume dependent, respiratory muscle activity is less likely to interfere with assessments at raised lung volume than if using the tidal volume range. Third, measurements of forced expiratory volume within a given time (FEV_t) are available and are considered the most powerful parameters to assess respiratory function in older children and adults (Figure 6). Another advantages are that flow limitation is more likely to be achieved in healthy infants, and that data reflect a more complete passive expiration. On the other hand, the raised volume forced expiration also has several disadvantages over the RTC technique (18, 35): First of all, extra equipment is needed, including an air pump, a relatively complex valve system, and a pneumotachograph and pressure transducer designed for large shifts in pressure, to avoid flow artefacts. Second, with pressures over 2 kPa or 20 cm H_2O, air leaks between the mask and the face are more likely to occur, and air may be forced down the oesophagus and gastric distension may occur. Third, infants are more likely to wake up as compared to the tidal volume forced expiration (personal communication A.F. Hoo)

Data

Since forced expiration is frequently completed in less than 1 second in infants, values of $FEV_{0.5}$, $FEV_{0.75}$ or FEF_{25-75} have been reported rather than FEV_1 in this age group (35) (Figure 6). Intrasubject variability of these FEV_t parameters derived from the raised volume technique is usually less than 5% and therefore much lower than for $V'max_{FRC}$ from the tidal method (40). However, a recent study showed a lower coefficient of variation for the $V'max_{FRC}$ than for the FEF_{75}; 6.3% and 8.9%, respectively (33, 41). Furthermore, FEV_t parameters are thought to distinguish better between normal and abnormal lung function (18, 42-44) and the effect of bronchodilators (45). Hence, assessing airway patency by means of the RVRTC technique is promising but has not yet proved to be superior over the tidal RTC technique (41).

Some studies suggest that in infants the RVRTC technique provides better assessments of airway function than its tidal volume counterpart (42, 43, 45). It has been suggested that the RVRTC technique is more reproducible and sensitive than partial flow volume curves and may provide data comparable to those obtained from spirometric measurements in older subjects, such as FVC, FEV_t, and FEF% (42, 43, 46-49). Recently, the London Collaborative CF Group con-

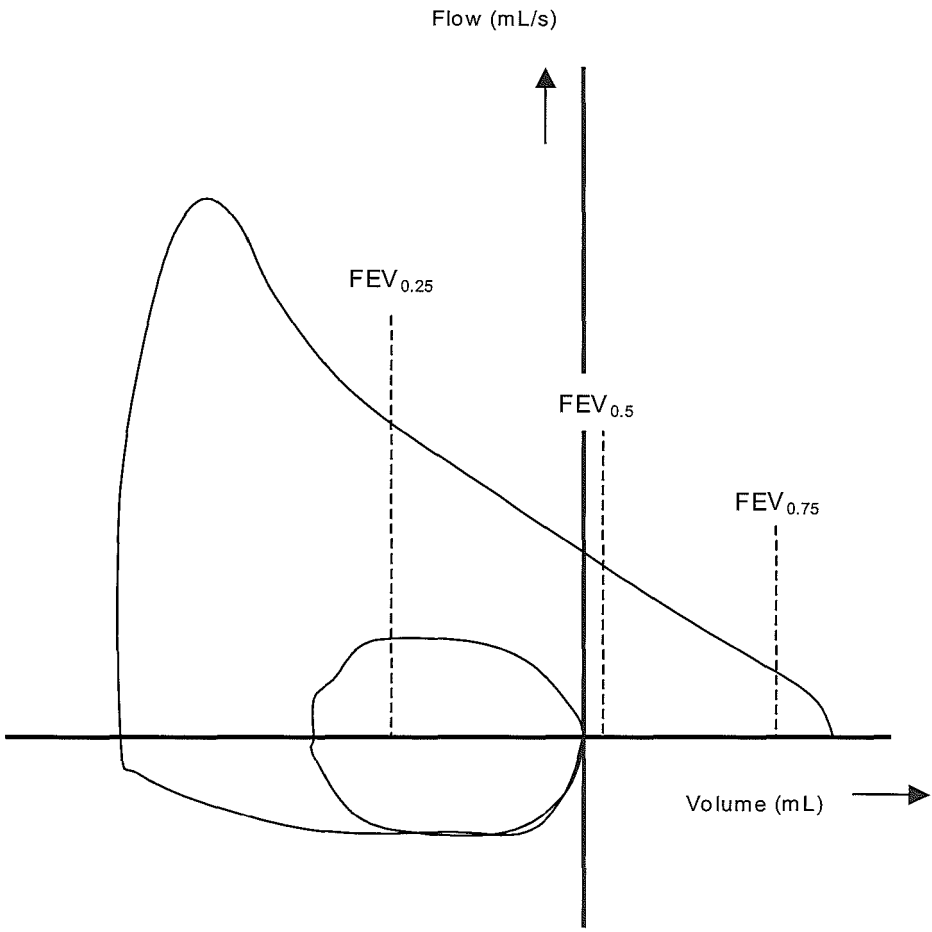

Figure 6. Example of fprced expiratory flow-volume curve obtained using the RVRTC technique. FEV_t: Forced expiratory volume at time t.

cluded that the RVRTC technique showed diminished airway function in infants with CF irrespective of a prior clinically recognised lower respiratory illness (43, 49), and that the RVRTC technique identified diminished airway function more frequently than the tidal RTC technique (43). In addition, the RVRTC technique could distinguish between a symptomatic and an asymptomatic period in infants with recurrent wheeze, whereas the tidal RTC technique could not (44). However, the RVRTC technique remains nonstandardised with respect to equipment, methodology, or analysis, making comparisons of data collected in different centres difficult (35). Further evidence is required as to whether this more complicated approach will prove to be more sensitive than RTC in detecting changes in airway function or response to therapy in infants (24).

2.3.3 Summary of forced expiration

Tidal volume forced expiration by means of the rapid thoracoabdominal compression technique is the first non-invasive technique in infants, which produces a partial flow-volume curve and allows measurement of $V'max_{FRC}$. Although the technique is limited due to a relatively high degree of variability and potential failure to achieve flow-limitation in healthy infants, it is the most commonly used technique to assess flow-volume curves in infants. The tidal volume forced expiration technique is standardised, allowing to compare data between centres, develop or use reference data or participate in multicentre trials which use parameters of infant lung function testing as outcome measures (3). In contrast, the RVRTC technique is not standardised since it lacks consensus (3, 35). In this thesis, we therefore chose to assess flow-volume curves by means of the tidal volume forced expiration technique.

2.4 Other measurements of Lung Function in Infants

Exhaled nitric oxide

Fractional exhaled nitric oxide concentration (FE_{NO}) is used as an inflammatory marker in asthma, where it may be useful in diagnosis and perhaps monitoring of treatment (50). Nitric oxide (NO) is derived from NO synthase enzymes (NOS), of which inducible NOS (iNOS) may have the greatest level of activity. Pro-inflammatory cytokines, which play a role in asthmatic inflammation, induce the expression of iNOS in cultured human airway epithelial cells. An increase in FE_{NO} in asthmatics may therefore be derived from an increased

expression of iNOS (51). Further evidence for this is the observation that corticosteroids inhibit induction of iNOS in epithelial cells (52) and in bronchial biopsies of adult asthmatics (53), and that they also reduce exhaled NO concentrations in asthmatic patients (54).

Measurement of FE_{NO} in adults and children is ideally performed by means of a single breath on-line measurement in accordance with American Thoracic Society (ATS) guidelines (55). In short, inspired gas should contain low NO (< 5 parts per billion (ppb)). The subject inspires to TLC and exhales at a constant flow of 50 mL/s until a plateau of ≥ 2 s can be identified. The expiratory pressure should be maintained between 5-20 cm H_2O in order to close the velum to avoid contamination with nasal NO.
In infants it is difficult to measure FE_{NO} according to ATS guidelines. Measurement of exhaled NO in infants is mostly performed when the infant is asleep, with or without the use of sedatives, during tidal breathing. Nevertheless, it could be an important diagnostic test to help identify infants who wheeze as a consequence of chronic airway inflammation, and would possibly allow for better targeting of inhaled corticosteroids in this age group (51). In one study, FE_{NO} has proven to be superior to baseline lung function and bronchodilator responsiveness in identifying preschool children with probable asthma (56). Exhaled NO levels in infants can be determined during tidal breathing or using the single-breath technique:

Tidal breathing techniques:
Both on-line and off-line methods are used in infants and neonates, with or without the use of sedatives.
On-line measurement of FE_{NO}:
Infants breathe into a face mask that covers the mouth and nose, or only the mouth. Teflon tubing is connected to a NO-analyser via a small hole in the mask or a side port in the expiratory part of a valve system. NO concentrations are recorded during different phases quiet tidal breathing (51). Although the reproducibility of this technique has shown to be satisfactory, there is limited experience with on-line tidal NO measurements in infants and young children (57).
Off-line measurement of FE_{NO}:
Exhaled air can be collected via a face mask, which covers the mouth and nose, which is connected to a non-rebreathing valve that allows inspiration of NO-free air from a NO-inert reservoir to avoid contamination by ambient NO. Exhaled breath samples are collected in a NO-inert bag fitted with the expiratory port once a stable breathing pattern is present (Figure 7) When the face mask does

not cover the nose, the expiratory port of the valve provides an expiratory resistance, resulting in an airway opening pressure that exceeds 2 cm H_2O (58) to avoid contamination with nasal NO. However, such a measurement is difficult to perform as infants breath mainly nasally.

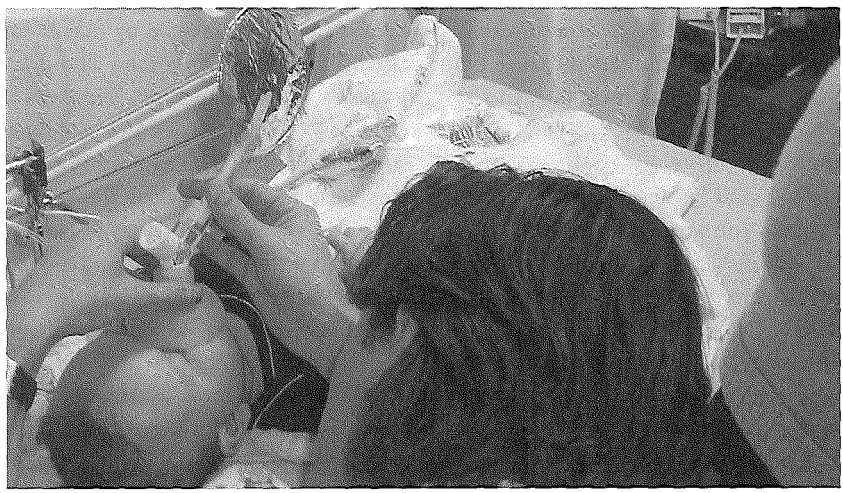

Figure 7. Off-line measurement of exhaled NO during tidal breathing.

The disadvantage of NO-measurements during tidal breathing in infants is that the mixed expiratory air is contaminated by ambient NO and nasal NO. Contamination with ambient NO can easily be avoided by using NO-free air when ambient NO > 10 ppb, or ambient air when ambient NO ≤ 10 ppb (55). When using NO-free air, measurements should be made after ten breaths in order to permit wash-out of dead space and lungs (58). Concerning the nasal NO, it is suggested that nasal NO concentrations are higher than lower airway NO, particularly in new borns and young infants (57, 59, 60). Therefore, upper airway NO contamination could have a significant impact on mixed exhaled NO concentrations in infancy, although the paranasal sinuses, that produce high NO levels in older children, are less well developed. Another disadvantage of NO-measurements during tidal breathing is that the variable expiratory flow will produce a scatter of exhaled NO (58). There are no data on the precise impact of sedation on exhaled NO. If the measurement of exhaled NO is performed as a part of an infant lung function testing, we suggest to perform the measurement at the beginning, before other measurements are done, as spiro-

metry can produce a fall in mixed expired NO in adult asthmatics (61).

Single-breath technique:
A modification of the raised volume RTC technique (see paragraph 2.3.2) has been used to measure FE_{NO} during a single forced exhalation (62). After passive inflation to a preset pressure of 20 cm H_2O, thoracic compression with an inflatable jacket caused forced expiration to occur through a face-mask with an expiratory flow resistor attached. During the forced expiration, the jacket pressure was increased manually to maintain a constant driving mouth pressure and hence a constant expiratory flow (50 ml/s). NO levels were measured online and the plateau of NO achieved. There is limited experience with this technique in infants, and it is currently unclear how this technique compares with the tidal-breathing techniques in the same age range, or to single-breath technique in older children and adults (51).

Passive respiratory mechanics
Passive respiratory mechanics describe the total resistance of the respiratory system (R_{rs}) (chest wall, lung tissues and airways combined). The measurement depends on the absence of respiratory muscle activity. If an infant's airway is briefly occluded, the Hering-Breuer inflation reflex (HBIR) (see 2.3.2) may be induced, resulting in a brief respiratory pause during which a relaxed airway pressure may be recorded, such that the difference in pressure at the airway opening reflects the elastic recoil pressure of the respiratory system. This forms the basis of the 'occlusion techniques', of which various adaptations have enabled passive respiratory mechanics to be assessed in infants and young children (2). When using the multiple occlusion technique (MOT), several occlusions are made at different lung volumes during expiration with the slope of the resultant volume-pressure plot representing the total respiratory system compliance (C_{rs}). The single breath technique (SBT) involves occluding the airway and invoking the HBIR to relax the respiratory muscles at end-inspiration. Pressure during this occlusion is measured and after removing the occlusion a 'passive' expiration follows, during which it is assumed that respiratory muscles remain relaxed. The slope of the flow-volume relationship during this 'passive' expiration is the expiratory 'τ_{rs}' (Figure 8) (2).

Extrapolation of the slope of the flow-volume profile to zero flow (C) allows estimation of the total volume that would be exhaled if the infant if the infant emptied to the elastic equilibrium volume (EEV) of the respiratory system. Compliance is calculated from the ratio of the volume above EEV at which the

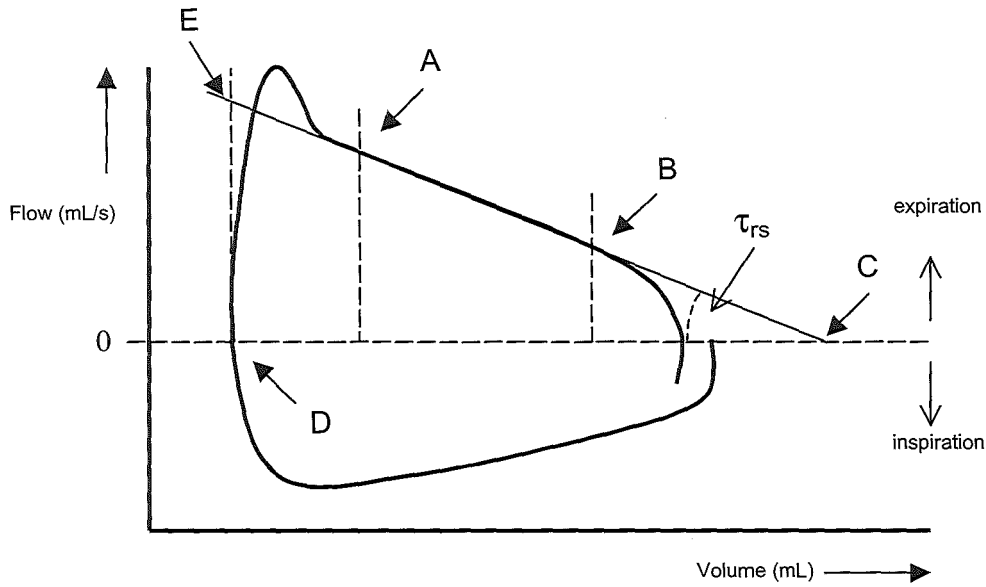

Figure 8. Single-breath technique analysis. Occluded at turn into expiration. A and B: points between the slope of the flow-volume relationship is calculated (τ_{rs}). C: extrapolated τ_{rs} -slope (AB). D: release of occlusion. E: extrapolated τ_{rs} –slope to release of occlusion (D). Figure modified from Fletcher et al (2)

occlusion was made (E) to the end-inspiratory recoil pressure at this volume. Resistance is then calculated by relating τ_{rs} to the measured compliance ($\tau_{rs} = R \cdot C$), assuming both a linear relationship over the volume range measured and relaxation of the respiratory muscles during expiration (2).

All occlusion techniques assume that, during airway occlusion, pressure at the airway opening reflects the elastic recoil of the respiratory system. This will only be the case if here is complete relaxation of all respiratory muscles during occlusion and there is complete equilibration of pressures throughout the respiratory system (2). The theory on which the single breath technique is based also assumes that the respiratory system is a linear, single-compartment, model. That is, the respiratory system can be represented by a single balloon on a pipe, with only two parameters, the elastance of the balloon and the resistance of the pipe. Furthermore it assumes that both compliance and resistance remain constant throughout expiration over the tidal range so that the respiratory system can be described by a single expiratory time constant (τ_{rs}) (2).

Dynamic pulmonary mechanics

The dynamic mechanics of the respiratory system describe the mechanical behaviour of the lungs, airways and chest wall throughout the breathing cycle, i.e. studies the pressures acting on the respiratory system and the changes in flow and volume that they produce (63). During the respiratory cycle both pleural (P_{pl}) and alveolar pressures (P_A) change. At the beginning of inspiration, when there is no airflow and hence no pressure drop along the airways, P_A equals the barometric pressure (P_B) which is zero. During inspiration, the thorax is expanded resulting in a lowering of P_A, initiating inspiratory airflow. Gas then flows into the lungs until P_A again equals the barometric pressure (P_B). The magnitude of the change in P_A depends on the magnitude of the airway resistance and the flows achieved: Pressure = Resistance x Flow, or $P = R \cdot V'$. Pleural pressure is sub-atmospheric at the beginning of an inspiration due to the elastic recoil of the chest wall. During inspiration, P_{pl} has a further drop in subatmospheric pressure due to the pressure required to overcome the flow and tissue resistive (i.e. frictional) forces of the lungs (P_{res}), but also the elastic forces of the lungs (P_{el}). Hence, at any moment in time,

$\Delta P_{pl} = \Delta P_{res} + \Delta P_{res}$

The magnitude of the change in P_{el} depends on both the extent to which the lung is inflated (i.e. change in inspired volume: ΔV) and the stiffness (elastance: E) of the lung:

$\Delta P_{el} = \Delta V \cdot E$

In a single-compartment, linear model, ΔP_{res} is proportional to airflow ($\Delta P_{res} = R \cdot V'$), whereas ΔP_{el} was known to be proportional to changes in lung volume (ΔV). It is possible to separate these components using for example pressure-volume diagrams (Figure 9), in order to calculate lung resistance, and dynamic elastance, or compliance which is the reciprocal of elastance. Therefore, dynamic pulmonary mechanics describe the lung resistance (R_L) (airways plus lung tissues) (63).

During expiration, the stored P_{el} is used to return the lung to its resting volume. The inward recoil of the lung results in a rise in alveolar pressure, thereby creating the driving force for expiratory flow until P_A again equals P_B. Also during expiration $\Delta P_{pl} = \Delta P_{res} + \Delta P_{el}$. However, P_{pl} will be less negative than the expected elastic component only, by an amount that is equivalent to P_{res}, that is the pressure to overcome lung and airway resistance during expiration. Hence, the shape of pressure-volume curves provide important information regarding the relative contribution of resistive and elastic forces of an infant's lungs (63).

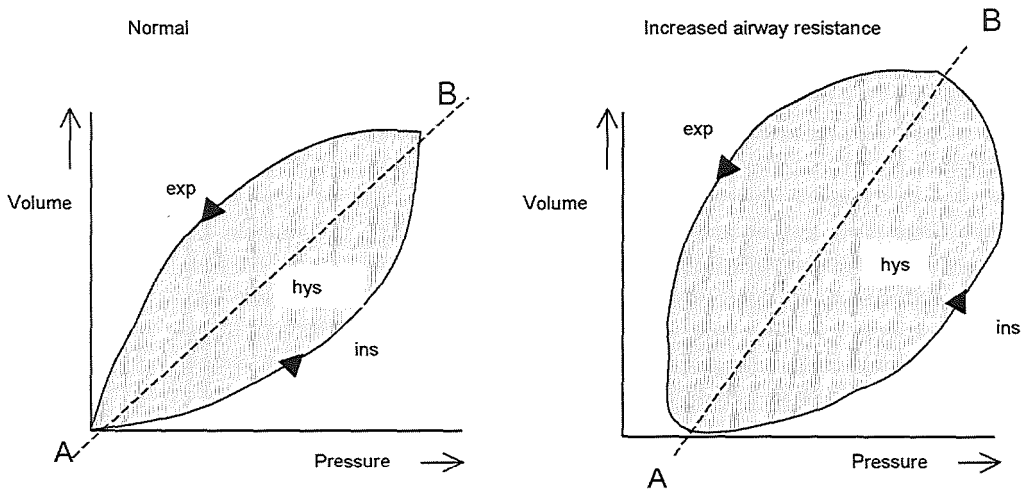

Figure 9. Pressure-volume diagrams. The left figure shows a normal pressure-volume diagram.The right figure shows a pressure-volume diagram in case of increased airway resistance. Ins: inspiration. Exp: expiration. Hys: hysteresis, the area of the pressure-volume loop.

Dynamic lung compliance ($C_{L,dyn}$) equals the change in volume divided by the change in pressure between points of flow-reversal, as shown by the slope of the dotted line A-B (Figure 9). This slope of the lung compliance also represents the pressure to overcome elastic forces (P_{el}), which is in phase with volume and hence forms a closed pressure-volume loop. As a result, $C_{L,dyn} = \Delta V / \Delta P_{el}$. The extent to which P_{pl} is more negative than P_{el} during inspiration, and more positive than P_{el} during expiration reflects the pressure required to overcome the frictional resistance of airways and lung tissues (P_{res}), and results in the hysteresis of the pressure-volume diagram (63). The lung resistance (R_L) is then calculated by dividing ΔP_{res} by ΔFlow, or $R_L = \Delta P_{res} / \Delta V'$. Dynamic lung mechanics can also be calculated using the mid-iso-volume approach, by relating changes in transpulmonary pressure (P_{tp}) to corresponding changes in flow (V') and volume (V) throughout the respiratory cycle (63). The transpulmonary pressure (P_{tp}) is the pressure at the airway opening (P_{ao}) minus the pleural pressure (P_{pl}). The P_{pl} may be estimated from oesophagal pressure because of the close apposition of the flaccid oesophagus to the pleural space (64). During quiet breathing, the changes in P_{pl} generated by the respiratory

muscles during inspiration occur in the negative direction and are in the order of 0.6 kPa. These pressure changes increase if tidal volume increases, and also in the presence of decreased lung compliance or increased pulmonary resistance (64). There are 3 different techniques to measure oesophagal pressure in infants: oesophagal balloon manometry, fluid manometry (liquid filled catheter) and solid-state micromanometry. In infants, mainly oesophagal balloon manometry is used. A catheter-mounted balloon containing a small but known volume of air is lowered into the lower third of the oesophagus to measure intra-oesophageal changes in pressure and volume.

Resistance measurements

There are several ways to measure pulmonary resistance in infants. As described earlier, pulmonary resistance can be measured by means of passive respiratory mechanics or dynamic pulmonary mechanics. In addition, resistance can also be measured plethysmographically or by means of the interrupter technique. We will briefly discuss these two methods.

Plethysmographic measurement of resistance

In contrast with resistance measurements by means of passive or dynamic lung mechanics, whole-body plethysmography assesses the resistance of the airways alone (R_{aw}). One of the advantages of the plethysmographic technique is that resistance can be measured throughout the respiratory cycle and valuable information can be obtained by inspecting the shape of the pressure-flow curves. Furthermore, since measurements are made during tidal breathing, assessments of any lung function abnormalities are performed under dynamic conditions, which may provide different information from that obtained at raised lung volumes or under passive conditions (12). Plethysmographic measurement of the R_{aw} is based on pressure fluctuations throughout the respiratory cycle, which result from gas compression/expansion within the lung due to the resistance of the airways. To eliminate volume variations due to changes in gas composition of the respired gas (CO_2, O_2, N_2), the inspired gas must be warmed and humified to body temperature and pressure under saturated conditions (BTPS). Airway resistance is then measured by relating the pressure difference between the alveoli (P_A) and the airway opening (P_{ao}) to the corresponding flow through the airways (12). Hence, $R_{aw} = (P_A - P_{ao}) / \text{Flow}$. Airway conductance ($G_{aw}$), the opposite of resistance, can be calculated by dividing 1 by the airway resistance: $G_{aw} = 1 / R_{aw}$. However, resistance is dependent on the inflation level of the lungs. Therefore, the conductance is corrected for lung volume resulting in the specific conductance or resistance ($sG_{aw} = G_{aw} / FRC$, or $1 / (R_{aw} \cdot FRC)$.

Interrupter technique

Measurements of the respiratory system using the interrupter technique requires quiet breathing and little cooperation. Interrupter technique measurements are based on measurements of tidal airflow and mouth pressure before and directly after closure of a fast shutter near a pneumotachograph. The ratio between pressure difference and airflow equals the interrupter resistance (R_{int}). After equilibration of pressure within the airways, when mouth pressure equals alveolar pressure, R_{int} reflects airway resistance (R_{aw}) (65). Validation studies against R_{aw} measured plethysmographically showed satisfactory results (65, 66). In preschool children, R_{int} measurements have proven to be sensitive by detecting changes in airway calibre in children who developed mild respiratory tract infections, by monitoring the effect of interventions and by identifying subgroups with mild respiratory symptoms among children from a general population (65, 67, 68). Together with a good within-occasion repeatability and interobserver agreement, the interrupter technique has proven to be a reliable and practical test of airway function in preschool children for whom reference values have been developed (65, 68, 69). However, the between-occasion repeatability for R_{int} measurements is too poor for intra-individual detection of changes (68). These reference values were based on children of 2 years of age and older using a mouth piece. Below that age measurements can only be conducted using a face mask (65). During infancy, R_{int} measurements are feasible in spontaneously breathing sedated and unsedated infants (Figure 10) (25, 70). Hall and co-workers studied the influence of facemask types and analysis techniques on the R_{int} in unsedated sleeping infants (70). Measurements made using a large volume, compliant face mask significantly underestimated R_{int}, while the choice of analysis method significantly influenced the variability and magnitude of R_{int}. They concluded that studies are needed to standardise equipment and to identify the most appropriate analysis technique for the age group of 0 to 2 years (70). Chavasse and co-workers compared R_{int} measurements with resistance measurements using the single breath occlusion technique (R_{rs}) and with $V'max_{FRC}$ in sedated infants (25). They concluded that R_{int} measurements are closely related these other measures of airway obstruction commonly used in infants. However, values obtained for R_{int} were markedly lower than for R_{rs}, but showed a strong correlation. This is possibly the result of R_{int} being a measure of airway resistance, while R_{rs} gives a measure of resistance of the entire respiratory system (i.e. airways, lung tissue and chest wall). In addition, R_{int} correlated negatively with $V'max_{FRC}$. It is recommended to report the median R_{int}, as it is less affected by outlying values (71).

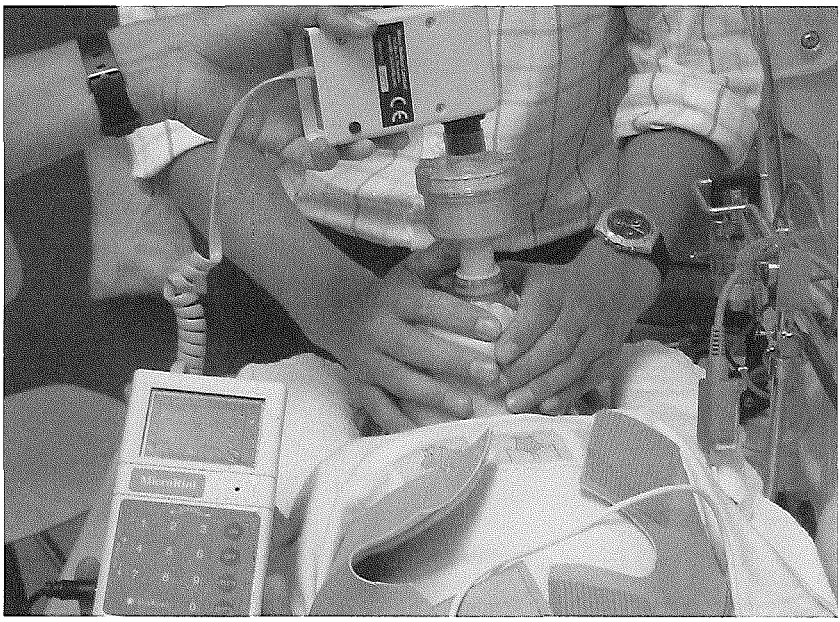

Figure 10. Resistance measurement using the interrupter technique (R_{int}) in a sedated infant.

Tidal breathing parameters

An infant's breathing pattern measured during tidal breathing contains significant physiological information pertaining to a number of processes related to respiratory control and pulmonary mechanical function (72). The most common used parameters are the tidal volume (TV), breathing frequency (BF), and the time to reach peak expiratory flow (t_{PTEF}) as a proportion of total expiratory time (t_{PTEF}/t_E) (Figure 11). For a healthy infant, between 3 and 12 months of age, the t_{PTEF}/t_E ranges between 0.26-0.29 (73). In obstructive airway disease the time to reach the peak tidal expiratory flow is shorter, and the duration of the expiration is longer as compared to healthy controls, leading to an decreased t_{PTEF}/t_E ratio. The index t_{PTEF}/t_E has been demonstrated to be useful in predicting wheezy illness in the newborn (74), in discriminating between asthmatic and non-asthmatic children (75-77), and between healthy controls and children with cystic fibrosis (77) and showing response to histamine, metacholine or salbutamol in asthmatic children (75-78), though t_{PTEF}/t_E has not found to be useful in the diagnosis of narrowed airways in infants (79-81). However, knowledge regarding the biological development and clinical/diagnostic value

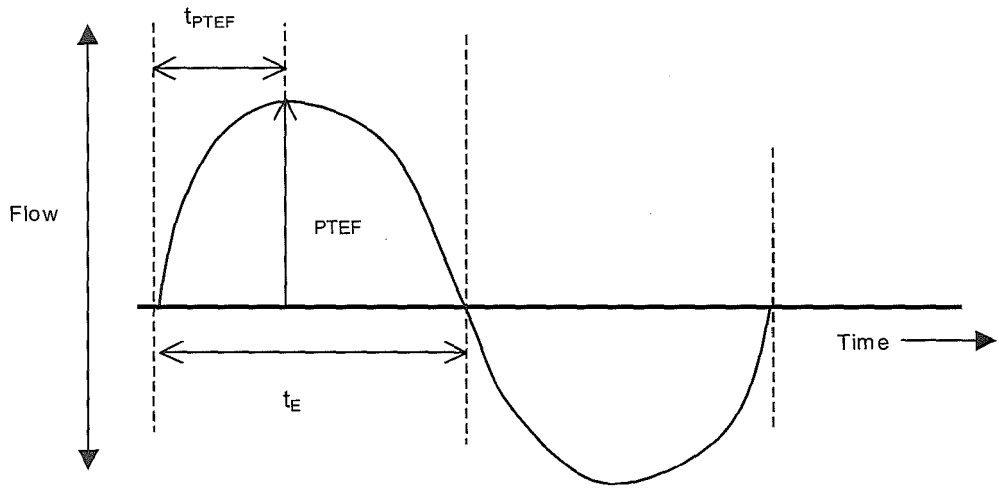

Figure 11. Measurement of expiratory tidal breathing parameters. t_E: Total expiratory time. PTEF: Peak tidal expiratory flow. t_{PTEF}: time to reach peak expiratory flow. t_{PTEF}/t_E: Time to reach peak expiratory flow as a proportion of total expiratory time.

of most tidal breathing parameters remains sparse. Moreover, the reference data that have been published are highly specific to the equipment used and the population studied and cannot be recommended for general use. Therefore, there is a need to establish reference ranges for t_{PTEF}/t_E so that it can be used more effectively in the clinical setting (72).

3. Clinical applications of Infant Lung Function Testing

Assessing $V'max_{FRC}$ by means of the RTC technique has been used to quantitate abnormalities of lung function in infants with respiratory disorders. Several studies used the $V'max_{FRC}$ as the primary outcome measure to:

- Determine normal physiologic growth and development of the infant respiratory system (20, 82, 83)
- Quantitate abnormalities of lung function in infants with respiratory

disorders, such as:
- recurrent wheeze
- cystic fibrosis
- neonatal chronic lung disease, or bronchopulmonary dysplasia
- anatomical abnormalities
- infants treated with extracorporeal membrane oxygenation

- Evaluate treatment regimes, such as:
  - Bronchodilator effect (84-93)
  - Inhaled steroids (94, 95)
  - DNAse (96)

- Assess bronchial responsiveness to inhaled pharmacological agents (32, 95, 97-106)

- Determine the influence of factors such as:
  - lower or upper respiratory tract infections (74, 101, 107, 108),
  - gender (5, 109, 110),
  - maternal smoking (111-113)
  - an atopic family history on infant pulmonary mechanics (100, 114)

  in epidemiological studies.

We summarised the results of lung function testing in infants with wheeze, cystic fibrosis, neonatal chronic lung disease, a large airway obstruction, infants following a treatment with extracorporeal membrane oxygenation and infants following repair of oesophageal atresia and tracheoesophageal fistula. When applicable, evaluation of treatment regimes are discussed. The influence prenatal and postnatal tobacco smoke exposure on lung growth and lung function in infants is also discussed.

3.1 Infant Lung Function Testing in Wheezy infants

Recurrent episodes of wheezing are a common problem in approximate 30% of all infants (age 0 to 3 years) (115-117). Infants who have respiratory illnesses with wheezing in the first year of life have lower levels of lung function before any lower respiratory illness develops, compared to infants without wheezing (74, 119). Therefore, it is thought that in the majority of infants with wheezing during the first year of life there is a transient condition of early life reduced

small airway calibre, which improves with time. Consequently, in a substantial minority of these infants wheezing episodes are probably related to a predisposition to asthma (118, 119). Wheezing that begins or persists into the second year of life may be part of the clinical entity recognized as asthma (119). In follow up of wheezy infants, 20% persisted to wheeze at the age of 4 years. This group of persistent wheezers had significantly lower $V'max_{FRC}$ at initial evaluation than infants who became asymptomatic (120). These findings suggest that during the first year of life, small airways predispose many infants to wheezing in association with common viral infections (74, 118-120).

Evaluation of treatment regimes

Most infants with recurrent episodes of wheezing are treated as adult asthmatics, with beta2-agonists and inhaled steroids as first choice medication (121, 122). However, there is no conclusive data on the effectiveness of these therapies in infants. Regarding the treatment with bronchodilators for wheezy infants, there are studies showing a beneficial effect (87-89), studies showing no effect (90-93), and studies showing an adverse effect on lung function and/or clinical variables (84-86). It seems plausible that contradicting findings are due to differences in lung function methodology, mode of aerosol administration or aetiology of airway obstruction. Recently, a Cochrane systematic review concluded that there is no clear benefit of using beta2-agonists in the management of recurrent wheeze in the first two years of life, although there is conflicting evidence (123).

Data on treatment of infants with recurrent wheeze with inhaled corticosteroids also lack consistency. There are studies showing a positive effect of inhaled steroid treatment on symptom scores (124-128), and one study showing no effect (129) (Table 2). Data from studies using subjective outcome measures to determine the effectiveness of inhaled steroids in infants with recurrent wheezing are equivocal. To our knowledge, only three studies evaluated the effectiveness of inhaled steroids in wheezy infants using pulmonary function (94, 95, 130). Maayan and co-workers investigated lung function in 9 infants with persistent wheezing, before and after two weeks of treatment with either inhaled steroids or placebo in a randomised, double blind, crossover trial. Two weeks of placebo treatment had no significant effect on lung function. After two weeks of inhaled steroid treatment $V'max_{FRC}$ increased, only the difference did not reach significance (94). Stick and co-workers evaluated lung function ($V'max_{FRC}$) and symptoms in 38 infants with recurrent wheezing, before and after 8 weeks of treatment with either inhaled steroids or placebo in a randomised, double blind trial. $V'max_{FRC}$ and symptoms improved for both groups

of infants during the study, but only in the placebo group the improvement in $V'max_{FRC}$ reached significance. There was no significant difference between the groups before or after treatment (95). Kraemer and co-workers compared 3 different treatment groups: 9 children were assigned to receive inhaled steroids combined with salbutamol on a dialy basis, 8 children received only salbutamol daily and 6 children received placebo (130). After a 6 weeks treatment period, symptom scores, thoracic gas volume (TGV), airway conductance (G_{aw}) and specific airway conductance (sG_{aw}) were compared between groups. There was a significant improvement in symptom scores, as well in all lung function parameters in the group treated with inhaled steroids combined with salbutamol when compared to the placebo group. In contrast, no significant differences were found between the group treated with inhaled steroids combined with salbutamol compared to the salbutamol-only group and/or the salbutamol and placebo group. Authors concluded that in wheezy infants inhaled steroids improve clinical status and lung function, when given in combination with salbutamol (130). Unfortunately, no conclusion about the effectivity of inhaled steroids alone, possibly in combination with salbutamol on demand, may be drawn. Regarding the effectiveness of inhaled steroids in wheezy infants on symptom scores, there are studies showing a positive effect of inhaled steroid treatment in wheezy infants (124, 125, 131, 132), and studies showing no such effect (95, 133).

In conclusion, there is no proven benefit of the treatment with beta2-agonists and/or inhaled steroids in the management of recurrent or persistent wheeze in the first two years of life. Further studies are needed to evaluate these treatment regimes in infancy, which are prescribed on a large scale without evidence based arguments.

3.2 Infant Lung Function Testing in Cystic Fibrosis

Measurement of lung function plays a central role in the management of patients with cystic fibrosis (CF), by evaluating the severity and progression of the disease and response to therapeutic interventions. In infants, measurement of lung function may be even more relevant as inflammation and infection may develop early in life and may be present without clinical signs (24, 134). Moreover, any damage sustained during these periods of rapid lung growth and development is more likely to have long-term adverse effects (24). Nevertheless, the role of infant lung function testing during infancy in CF

Table 2. Details of other studies of inhaled steroids in infants. All studies are randomised placebo controlled trials. BUD: Budesonide. BDP: Beclomethason dipropionate. FP: Fluticasone propionate. Salb: Salbutamol. *: The study by Maayan and co-workers (94) is mentioned twice as they found a positive effect of inhaled steoids on symptom scores, but no such effect on lung function. ¶: Note that in the study by Kraemer et al (130) salbutamol was given on a regular base. BDP + Salb was effective versus placebo. However, no significant differences were found between the BDP + Salb and salbutamol group and/or the salbutamol and placebo group.

Study	N	Mean age (range) Months	Drug	Daily Dose	Device	Duration	Parameters
Effective							
• Maayan et al(94)*	9	6 (4-8)	BDP	1,5 mg	Nebuliser	2 wks	Symptoms
• Bisgaard et al(124)	77	24 (11-36)	BUD	800 µg	MDI+spacer	12 wks	Symptoms
• Noble et al(131)	15	11 (4-18)	BUD	300 µg	MDI+spacer	6 wks	Symptoms
• Connett et al(132)	40	20 (12-36)	BUD	400-800 µg	MDI+spacer	26 wks	Symptoms
• Kraemer et al(130)¶	29	12 (2-25)	BDP/Salb	300/600 µg	MDI+spacer	6 wks	Symptoms + Lung function
• Bisgaard et al(125)	237	28 (12-47)	FP	200 µg	MDI+spacer	12 wks	Symptoms
• Teper et al (128)	30	13 (6-24)	FP	100 and 200 µg	MDI+spacer	26 wks	Symptoms
Ineffective							
• Maayan et al(94)*	9	6 (4-8)	BDP	1,5 mg	Nebuliser	2 wks	Lung function
• Van Bever et al (133)	23	10 (3-17)	BUD	1 mg	Nebuliser	4 wks	Symptoms
• Stick et al(95)	38	12 (5-18)	BDP	400 µg	MDI+spacer	8 wks	Symptoms + Lung function
• Barrueto et al(129)	31	16 (14-18)	BDP	400 µg	MDI+spacer	8 wks	Symptoms

management remains unclear, and there is no conclusive evidence as to which test(s) may be best in identifying early changes, assessing response to treatment or predicting prognosis (24). We summarized lung function data in infants with CF, regarding lung volume, and airway patency assessed by the tidal RTC technique.

Lung volume in infants with CF

There is no consistency about the technique that should be used for measuring lung volume in infants with CF. In the presence of airway obstruction, which is the most prominent early manifestation of CF (134), gas dilution techniques may lead to underestimation of lung volume due to the presence of trapped gas. For whole body plethysmography, there can be an underestimation of alveolar pressure changes at the airway opening, particularly in the presence of obstructive airway disease, potentially resulting in overestimation of lung volumes (24). Studies that used plethysmography in infants with CF found increased FRC_p in at least subgroups of patients, and suggest that hyperinflation is one of the earliest features of CF (24, 26, 135-138).

Lung function in infants with CF

The most commonly reported method for assessing forced expiration in infants with CF has been the tidal RTC technique for measuring $V'max_{FRC}$ (43, 97, 108, 136, 137, 139-144). The natural course of pulmonary involvement in infants with CF before infection occurs and disease becomes clinically evident remains poorly understood (24). Although serial measurements of lung function are well known to be far more valuable than a single assessment (145), very little longitudinal data are available for infants due to difficulties in performing measurements frequently. Beardsmore and co-workers performed repeat measurements in 17 infants with CF during the first year of life (136). When retested most of the infants who had initially normal lung function had deteriorated with respect to both specific airway conductance (sGaw) and $V'max_{FRC}$. As $V'max_{FRC}$ was not affected before sGaw, the authors concluded that there is no functional evidence that small airways are the site of primary pulmonary involvement in CF. This conclusion was based on the assumption that small airway disease is best reflected by flow limitation at low lung volumes, i.e. $V'max_{FRC}$. However, there have been no attempts to correlate functional changes with pathological findings in young children with CF in order to clarify this statement (24). Tepper and co-workers performed lung function measurements at time of diagnosis and 12 months later. They found that $V'max_{FRC}$ was lower in infants presenting with respiratory symptoms compared to those without (142).

One study attempted to relate lung function during infancy to that obtained in childhood (26). Twenty-nine CF patients who underwent ILFT (FRC_p, $V'max_{FRC}$) were reassessed between 4 and 7 years of age using whole body plethysmograph and maximal forced expiratory manoeuvres (FVC, FEV_1, MEF_{50}, MEF_{25}). Although parameters obtained in infancy and at school age were not directly comparable, it was reported that lung function deteriorates before school age in most children, with a significant correlation between the FRC score in infancy and at school age. When $V'max_{FRC}$ scores were compared with FVC, FEV_1, MEF_{50}, or MEF_{25}, no significant relationship was found (26).

Evaluation of treatment regimes

The use of prophylactic oral antibiotic treatment in asymptomatic infants with CF is a controversial subject (24). Beardsmore and co-workers performed FRC_p and $V'max_{FRC}$ measurements at 3-4 months and 1 year of age in 42 infants enrolled in a prospective randomised controlled trial of antibiotics prophylaxis (137). No advantage was found with respect to lung function, but other criteria, such as fewer hospital admissions during the first year, led the authors to concluded that antibiotics prophylaxis is indicated in newly diagnosed infants with CF. Lung function in infants with CF following an in-hospital antibiotic treatment for pulmonary exacerbations was studied by Clayton and co-workers (144). For the group, there was a significant improvement in all lung function parameters before and after 2 weeks of antibiotic treatment. However, there was a considerable variability in response between infants, and improvements in $V'max_{FRC}$ were not necessarily accompanied by improvements in other lung function parameters (144). In contrast, in a randomised placebo controlled trial, Tepper and co-workers found no improvement in $V'max_{FRC}$ in 20 infants during a two week period of hospitalisation for pulmonary exacerbation, whether or not systemic steroids (n=10) were added to the conventional treatment, which included antibiotics (143). Since both this study and the study by Clayton and co-workers (144) used $V'max_{FRC}$ as an outcome variable and used similar reference values (146), it is not clear why such discrepant results occurred, other than the small numbers enrolled in each study which could have led to sampling bias (24, 96).

3.3 Infant Lung Function Testing in Neonatal Chronic Lung Disease

Chronic lung disease (CLD), or bronchopulmonary dysplasia (BPD), is a common sequel of mechanical ventilation and oxygen therapy in prematurely born

infants (147). Despite advances in prenatal and neonatal care, including antenatal and postnatal steroids, surfactant treatment and high-frequency oscillation ventilation (HFOV), CLD is still one of the major complications in mechanically ventilated premature infants (148). The overall incidence of CLD has remained high as a result of the increased survival of extremely premature infants, who are most at risk to develop CLD (148). Long-term studies show that survivors of CLD have abnormal pulmonary function tests at school age (149, 150), whereas infants who received initial HFOV showed normal lung function at school age (151). Only a few studies evaluated lung function during the first years of life in children with CLD. In young children with CLD, lung function parameters, such as functional residual capacity, compliance, resistance and conductance, show a gradual improvement towards the normal range during the first three years of life (152-154). On the contrary, three studies evaluated forced expiratory flows, which were found to be decreased during the first two years of life (152, 154, 155). In 1986, Tepper and co-workers studied 20 infants with CLD during the first year of life. The infants with CLD had lower absolute and size-corrected flows than control infants. In addition, the slope of the linear regression of $V'max_{FRC}$ versus length was significantly lower for the infants with CLD than for normal control infants, indicating poor growth of the airways. The authors concluded that, although infants with CLD improve clinically during the first year of life, they have abnormal functional airway growth (152). In 1997, Iles and Edmunds confirmed this finding by stating that in infants with CLD lung growth is well below that seen in normal lung growth during the first year of life, possibly as a result of lack of catchup growth and/or disease resolution (155). In 1997, Baraldi and co-workers studied 24 infants with CLD, weighing less than 1,250 g at birth, from birth until 2 yr of age (154). They described an improvement in most lung function parameters, including FRC, reaching the range of normal values at 2 yr of age. However, less favorable data of $V'max_{FRC}$ were found with individual values reduced more than 40% of predicted values in 70% of the children. They concluded that although pulmonary mechanics of CLD survivors improves during the first years of life, they still present a substantial airway function impairment as revealed by the low forced expiratory flows (154).

Due to advances in prenatal and neonatal care there is an increased survival of extremely premature infants, with very low and extremely low birthweights. Therefore, these results obtained in the past may not be valid for infants who develop CLD nowadays. There are no recent studies that evaluate forced expiratory flows during the first year of life in very low birth weight (VLBW) infants

with CLD, in the era of surfactant therapy and HFOV.

3.4 Infant Lung Function Testing in infants with a Large Airway Abnormality

Chronic or intermittent wheeze can be caused by anatomical abnormalities including malacia, stenosis or compression of larger airways. Infants with severe tracheobronchomalacia or compression of the larger airways are characterized by stridor, dyspnoea, life-threatening apnoeic spells and recurrent pneumonia (156-158). Airway malacia is a condition in which the airway is unusually collapsible, as a result of a weakness or deficiency of the cartilaginous elements of the airway wall, or from decreased tone of the myoelastic elements (159). Treatment of these infants with airway malacia may include aortopexy or long-term CPAP (160, 161). However, infants with mild or moderate symptoms may go unrecognised. They present themselves with chronic or persistent wheeze and often constitute a therapeutic dilemma for the paediatrician (156, 157, 162). When treatment with inhaled corticosteroids and/or ß2-agonists fails and symptoms persist, a bronchoscopy may be considered as the next diagnostic step (156). Bronchoscopy may reveal airway narrowing due to malacia or compression. However, bronchoscopy is an invasive procedure that requires general anaesthesia. Non-invasive objective criteria for anatomical abnormalities to identify infants for bronchoscopy are lacking. Lung function testing in infancy (ILFT) may help in identifying central airway obstruction. Only few studies investigated the association between lung function in infants and anatomical airway obstruction.

Panitch and co-workers studied the hypothesis that in infants with tracheomalacia, contraction of airway smooth muscle tone results in increased airway patency (i.e. $V'max_{FRC}$), and conversely, that administration of a bronchodilator results in a decrease in airway patency (86). In 3 patients with tracheomalacia, baseline $V'max_{FRC}$ was significantly below normal. As hypothesised, $V'max_{FRC}$ improved significantly after an increase in smooth muscle tone due to methacholine. In addition, $V'max_{FRC}$ returned toward or below baseline after administration of a bronchodilator (86). A possible explanation could be that airway mooth muscle tone is important for the compliance of the airway. Therefore, a reduction of smooth muscle tone by bronchodilation could make the airways more compliant, and therefore more collapsible, resulting in increased dynamic compression and reduced forced expiratory flows (21, 163). Tepper and coworkers evaluated the effect of operative correction of tracheal lesions on forced

expiratory manoeuvres in three infants (23). Preoperatively, all three demonstrated severe flow limitation with forced expiratory flow close to tidal expiratory flow. Postoperatively, the PEFV curves changed to a normal convex shape, and $V'max_{FRC}$ returned towards normal (23). They state that the shape of the PEFV curves can help to localize the site and quantitate the severity of the airway obstruction. However, further studies are required to evaluate the sensitivity of PEFV curves in detecting tracheal lesions in infants and the impact of this information upon the clinical management of these patients (23).

In a longitudinal study of lung function in a cohort of 252 healthy symptom-free term infants, Young and co-workers observed tidal flow limitation at 1 month of age in approximately 10% of the infants (164). All these tidal flow limited infants had a positive family history of asthma, atopy and/or parental smoking. At 6 and 12 months of age these infants no longer had tidal flow limitation. Nonetheless they had a significantly reduced lung function as compared to matched controls. Moreover, flow limitation in early life was associated with physician-diagnosed asthma at the age of 2 years (Odds ratio: 7.4). This led the authors to conclude that infants with abnormal lung function soon after birth may have a genetic predisposition to asthma or other airway abnormalities (164). From the same cohort, Turner and co-workers analysed the data from 3 to 11 years of age (165). Only at 4 years of age the group with tidal flow limitation had increased wheeze, and at 6 and 11 years they had increased airway responsiveness and reduced lung function, as compared with other cohort members. In contrast with the study by Young and co-workers (164), atopy and parental asthma were not increased in the group with tidal flow limitation. Therefore, Turner and co-workers suggested that flow limitation in early infancy may identify an at-risk group, different from asthma, who has reduced lung function and increased airway responsiveness in later life (165). From these studies it can be concluded that tidal flow limitation may be present in asymptomatic infants, and that the tidal flow limitation mostly resolves during the first year of life. Nevertheless, it is associated with an increased risk for respiratory illnesses, possibly different from asthma, later in life. Whether these respiratory illnesses are based on central airway abnormalities remains to be elucidated, as bronchoscopic investigations were not carried out in the patients of this Australian cohort. From these studies it may be concluded that tidal flow limitation in infants may be present without respiratory symptoms, and that tidal flow limitation mostly resolves during the first year of life. Nevertheless, it is associated with an increased risk for respiratory illnessses later in life. If these respiratory illnessses are based on asthma and/or other airway abnormalities remains to be elucidated.

3.5 Infant Lung Function Testing in infants following Extracorporeal membrane oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) is a supportive intensive-care technique used for newborn infants with acute reversible respiratory failure and a high mortality risk with conventional management. ECMO consists of a cardiopulmonary bypass while resting the lungs and using minimal ventilator settings. A schematic drawing of a venoarterial ECMO circuit is shown in figure 12.

It is thought that ECMO support promotes lung healing and prevents further injury from high oxygen concentration and barotrauma (166). The UK ECMO trial gave a survival advantage of ECMO over conventional management, without a concomitant increase in severe disability (167, 168). Since ECMO could potentially result in survival of infants with severe respiratory dysfunction who would otherwise have died, this would result in poorer respiratory status in the ECMO group. Alternatively, infants receiving ECMO might be spared aggressive ventilation and consequent barotrauma, which has been shown to be associated with subsequent alterations in respiratory mechanics (169). Therefore, investigation of the respiratory function of survivors is essential whether or not ECMO gives a survival advantage. Several groups studied respiratory function

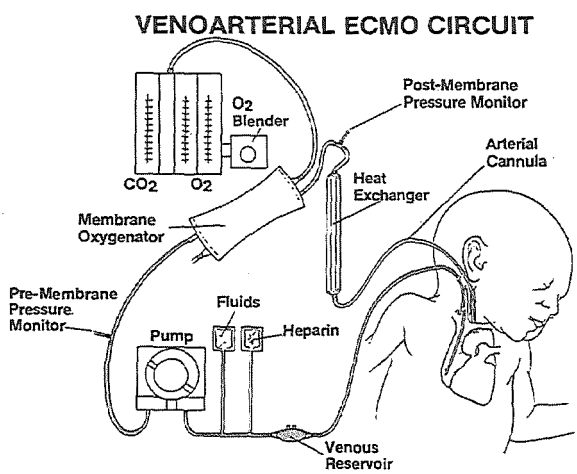

Figure 12. Schematic drawing of extracorporeal membrabe oxygenation (ECMO) circuit.

in infants during or shortly after ECMO (170-172), at 6 months (173) or at 12 months (169). These studies found a reduction in pulmonary function during the first year of life, confirming that ECMO does not prevent sequelae of severe respiratory disease in the newborn period (169, 172). Only two groups studied the $V'max_{FRC}$. Greenspan and colleagues (172) studied the $V'max_{FRC}$ after ECMO at approximately 1 month of age, which was approximately 108 mL/s. Calculation of $V'max_{FRC}$ in Z score using the normative data by Hoo and colleagues (5), was not possible since no information about length at time of measurement was provided. Beardsmore and colleagues (169) evaluated $V'max_{FRC}$ at 12 months of age in infants randomly assigned to receive either ECMO or conventional management. In the ECMO group, the $V'max_{FRC}$ was 170 mL/s or -1.63 SD (personal communication A. Hoo), using the normative data by Hoo and colleagues (5). There was a trend towards a lower $V'max_{FRC}$ in the conventional managment group, with a $V'max_{FRC}$ of 137 mL/s, or –2.0 SD. However, using the normative data by Sly and colleagues (3), which uses postnatal age as the independent variable, the $V'max_{FRC}$ in Z score is approximately –0.3 SD and –1.6 SD at 1 and 12 months, respectively.
In conclusion, these cross-sectional data from different studies suggest a decrease in forced expiratory flow during the first year of life in ECMO survivors, meaning ECMO support can not prevent sequelae of severe respiratory disease. Nonetheless, there is a trend towards a better $V'max_{FRC}$ in the ECMO group, as compared with the group who received conventional managment. Although serial measurements of lung function are well known to be far more valuable than a single assessment (145), longitudinal data are only available for infants during or shortly after ECMO (170, 171). To our knowledge, no study evaluated lung function longitudinally during the first year of life in ECMO survivors.

3.6 Infant Lung Function Testing in infants following repair of oesophageal atresia and tracheoesophageal fistula

Since the first successful primary repair of oesophageal atresia and tracheoesophageal fistula (OA-TOF) in 1941 (174), there has been a dramatic improvement in survival of infants with this condition (175). With reduced mortality, the importance of morbidity has become increasingly relevant. Variable respiratory and gastro-intestinal symptoms have been reported, mainly during the first 3 years of life (176, 177). These symptoms include cough, wheeze, gastro-oesophagal reflux, aspiration, recurrent pneumonias and dysphagia (178, 179).

In addition, children and adults who have undergone OA-TOF repair, are known to have lung function abnormalities (177, 180, 181). It is tempting to speculate that functional abnormalities of the upper airway or aspirations are the main causes of respiratory symptoms and dysfunction (178). However, it is not clear whether respiratory symptoms and abnormal lung function is in related with gastro-oesophagal complications (178, 180, 181).

Possibly, lung function measurements during infancy can elucidate this question as symptoms are predominantly present during the first 3 years of life. To our knowledge, there is only one study that assessed respiratory function in infants following OA-TOF. Beardsmore and co-workers studied 16 infants within 3 months after repair of OA-TOF (178). Seven infants had normal initial respiratory function tests. Of these 7 infants, six remained symptom-free or developed minor clinical symptoms and one infant developed stridor which improved spontaneously. The remaining 9 infants had abnormal initial respiratory function tests: one was symptom-free and the remainder developed respiratory and/or gastro-oesophageal symptoms. The functional abnormalities appeared to reflect the severity of the clinical problems encountered. It was concluded that infant lung function testing following OA-TOF repair may augment the value of clinical appraisal, help define post-operative respiratory status, and provide a general guide to likely clinical progress (178). Of this group of 16 infants, 14 were studied at school age for respiratory function and clinical problems (177). Mean values for the group as a whole showed reduced lung function. Respiratory function and clinical findings at school age appeared unrelated to status in infancy. Nonetheless, most patients showed a restrictive pattern of lung volume wich would appear to result from reduced lung growth after surgery. It was concluded that in children following OA-TOF repair, infant lung function testing is of limited value in medium term prognosis, but may aid in the management of contemporary slinical signs (177).

We believe that these limited data can not elucidate whether respiratory symptoms and abnormal lung function are related with gastro-oesophagal complications (178, 180, 181). To our knowledge, there is no structured follow-up of clinical and respiratory status in a larger group of infants following OA-TOF repair.

3.7 Application of Infant Lung Function Testing in Epidemiology: The effect of prenatal and postnatal tobacco smoke exposure on lung growth and lung function in infants and children

The adverse effects of passive smoking on the health of the foetus and child are thought to be common knowledge. Surprisingly, still 15-37% of women smoke while pregnant (182-184). Foetal breathing movements are essential for normal growth and structural maturation of the foetal lungs (185). In animal studies, prolonged absence or impairment of foetal breathing movements as a result of cigarette smoke during pregnancy, is likely to result in hypoplasia of the foetal lungs (185, 186) with fewer saccules (187).

These observations are likely applicable to humans since nicotine caused a reduction in the incidence of foetal breathing movements in normal and abnormal human pregnancies (188). Moreover, there is compelling evidence that maternal smoking reduces lung function in young children and that the effect is present at birth and attributable to effects of maternal smoking during pregnancy and early postnatal exposure on the child's lung development (189-192). In infants born to smoking mothers lung function tests show a reduction in forced expiratory flows as compared to infants born to non-smoking mothers (111-113, 192). This reduction in forced expiratory flows ($V'max_{FRC}$), could amount to 51% as compared to infants whose mothers did not smoke during pregnancy (111). The effect of prenatal smoke exposure most likely plays a greater role on lung function in childhood than postnatal and childhood exposure (193). However, it is difficult to resolve the role of prenatal smoking per se as prenatal smoking is almost invariably associated with postnatal smoking. How long the impaired lung function that results from exposure in utero continues to be significant is still not known (194). Therefore, smoking during pregnancy might affect adult lung function, which is suggested to be 'programmed' in foetal life (195). In a pooled analysis of school-aged children, exposure to environmental tobacco smoke (ETS) was associated with a reduction of 1.4% in forced expiratory volume in one second (FEV_1). Parameters for airway patency of the peripheral airways, the mid and end expiratory flow rates, show a decrease of respectively 5.0% and 4.3%, in those exposed to ETS (191). These small, but significant, deficits in spirometric indices are almost certainly causally associated with maternal smoking (191) and much of the effect may be due to maternal smoking during pregnancy and/or neonatal exposure (191, 193). Smoking by the father only had no significant effect on the children's lung function (191). A dose-response relationship was not always shown, perhaps due to the fact

that parents tend to smoke less as their children develop respiratory symptoms (191). When the independent effect of prenatal and postnatal tobacco smoke exposure on children's lung function was studied, the effect of maternal smoking during pregnancy was larger than that of current smoking (196). If this reduction in lung function due to passive smoking increases the risk for wheezing and/or asthma is not fully clear. However, prenatal maternal smoking increases the risk for symptomatic paediatric asthma (197) and postnatal maternal smoking is associated with an increased incidence of wheezing illness up to the age of 6 years (198). The reason why prenatal passive smoking is associated with symptomatic paediatric asthma, and postnatal passive smoking is associated with non-atopic 'wheezy bronchitis', remains to be elucidated. Possibly, a reduction in lung function as a result of prenatal passive smoking (111-113) makes the children more susceptible for respiratory symptoms and, therefore, enables the diagnosis of paediatric asthma. Furthermore, the distinction between wheezy bronchitis and asthma can be very difficult, and it seems conceivable that they can co-exist as well. Amongst children with established asthma, parental smoking is associated with more severe disease (198, 199).

In conclusion, lung function tests in infants and older children born to smoking mothers show reduced airway patency, probably reflecting underdevelopment of lungs and airways, where passive smoking before birth seems even more harmful than after birth. Therefore, passive smoking is an important risk factor for acute and chronic, sometimes even lifelong, morbidity that can easily be avoided.

Based on: Hofhuis et al. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. Arch Dis Child 2003 (200).

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General introduction and aims of the study

General introduction

In the past 20-25 years there has been an increase in interest in studying the respiratory system in infants (1). Especially in the last 5 years, when 62 peer-reviewed studies on lung function testing in infants have been published (2). A major part of these studies were performed for research purposes, such as physiologic research, pathophysiology of a disease, drug or therapy trials, or lung function methodology. These studies remain essential as the management of infants with lung disease cannot advance without adequate information on the way disease affects lung function and how it responds to treatment. Moreover, knowledge gained from clinical trials improve treatment in the long term (2). Therefore, studies performed for research purposes also have a large clinical impact. The minority of the published studies on lung function testing in infants were performed for clinical purposes, such as follow-up of disease or clinical managment. Moreover, there are no studies aimed to determine the clinical value of testing lung function in the management of the infant with a respiratory problem (2).

With the publication of standards and normal values for infant lung function testing (3-5), clinical applications of the lung function tests in infants have become more feasible. In the present thesis we studied lung function in infants with several respiratory disorders. In addition, we aimed to determine the clinical value of lung function testing in excluding or recognizing large airway abnormalities.

Study aims

Infants with recurrent or persistent dyspnea

There is no clear evidence that treatment with beta2-agonists and/or inhaled steroids in the management of recurrent or persistent dyspnea in the first two years of life is beneficial. Allthough no evidence based arguments exist for these treatment regimes, they are prescribed on a large scale. Further studies

are needed to evaluate these treatment regimes in infancy. Therefore, we aimed to evaluate the effect of bronchodilators (beta2-agonists) on the lung function in infants with recurrent wheeze and in infants with airway malacia (Chapter 3). Furthermore, we studied the effect of inhaled steroids on lung function in infants with recurrent wheeze, and aimed to identify subgroups of infants in which the treatment is more effective (Chapter 4).

Infants with chronic lung disease

Due to advances in prenatal and neonatal care there is an increased survival of extremely premature infants, with very low and extremely low birthweights. Therefore, lung function data obtained in the past may not be valid for infants who develop chronic lung disease (CLD) nowadays. There are no recent studies that evaluate forced expiratory flows during the first year of life in very low birth weight infants with CLD, in the era of surfactant therapy and HFOV. Therefore, we aimed to evaluate lung function longitudinally during the first year of life in premature born infants of very low birth weight with chronic lung disease (CLD), in the era of surfactant therapy and high-frequency oscilation ventilation (Chapter 5).

Infants with a large airway abnormality

There are no studies aimed to determine the clinical value of lung function testing in the management of the infant with a respiratory problem (2). Infant Lung Function Testing may help in identifying large airway abnormalities. Nonetheless, the predictive value of lung function parameters in excluding or recognizing airway abnormalities in wheezy infants is unknown. Therefore, we aimed to assess the predictive value of lung function parameters for excluding large airway abnormalities, diagnosed by bronchoscopy in a group of infants with chronic wheeze (Chapter 6).

Infants following ECMO support

Investigation of the respiratory function of survivors of extracorporeal membrane oxygenation (ECMO) support is essential to evaluate whether or not ECMO gives a survival advantage. Only few studies evaluated pulmonary function during the first year of life, confirming that ECMO does not prevent sequelae of severe respiratory disease in the newborn period. However, no study evaluated lung function longitudinally during the first year of life in ECMO survivors. Therefore, we aimed to evaluate lung function longitudinally during the first year of life in infants following ECMO support (Chapter 7).

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BRONCHODILATION IN INFANTS WITH MALACIA OR RECURRENT WHEEZE

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Arch Dis Child 2003;88(3):246-9

Abstract

Controversy remains regarding the effectiveness of bronchodilators in wheezy infants. We assessed the effect of inhaled β_2-agonists on lung function in infants with malacia or recurrent wheeze. The study aims were to assess the nature and magnitude of the bronchodilator response, and to determine whether a negative effect of β_2-agonists on forced expiratory flow ($V'max_{FRC}$) is more pronounced in infants with airway malacia, compared to infants with wheeze. We retrospectively analysed lung function data of 27 infants: 8 malacia, 19 recurrent wheeze. Mean (SD) age was 51 (18) weeks). Mean $V'max_{FRC}$ (in Z score) was assessed before and after inhalation of β_2-agonists. Baseline $V'max_{FRC}$ was below reference values for both groups. Following inhalation of β_2-agonists the mean (95% CI) change in mean $V'max_{FRC}$ in Z scores was -0.10 (-0.26 to 0.05) and -0.33 (-0.55 to -0.11) (p=0.006) for the malacia and wheeze group, respectively. We conclude that in infants with wheeze, inhaled β_2-agonists gave a significant reduction in mean $V'max_{FRC}$. Infants with malacia were not more likely to worsen after β_2-agonists than infants with recurrent wheeze.

Introduction

Bronchodilators are widely used for wheezy infants, despite conflicting data on their effectiveness. There are studies showing a beneficial effect of β_2-agonist

treatment in wheezy infants (1-3), studies showing no effect (4-7), and studies showing an adverse effect (8-10). It seems plausible that contradicting findings are due to differences in lung function methodology, mode of aerosol administration or aetiology of airway obstruction.
Airway malacia is a condition in which the airway is unusually collapsible, as a result of a weakness or deficiency of the cartilaginous elements of the airway wall, or from decreased tone of the myoelastic elements (11). It has been shown that reduction of smooth muscle tone makes the airway more compliant (12), and therefore more collapsible (13). In infants with intrathoracic tracheomalacia there is limited evidence to suggest that β_2-agonists cause deterioration in airway patency (10). Therefore, we hypothesised that a negative effect of β_2-agonists on airway calibre would be more likely and more severe in infants with airway malacia. The study aims were to assess the nature and magnitude of the bronchodilator response in infants with malacia or wheeze, and to determine whether a negative effect of β_2-agonists on forced expiratory flows is more pronounced in the infants with airway malacia.

Material and Methods

Subjects

We retrospectively analysed lung function data of infants with malacia or recurrent wheeze, who underwent infant lung function testing (ILFT) before and after the administration of β_2-agonist. Measurements were performed as part of our clinical routine between 1998 and 2000 at the outpatient clinic for paediatric respiratory medicine of the Sophia Children's Hospital. The study population consisted of 27 infants (19 boys); 8 infants had airway malacia, and 19 infants had aspecific recurrent wheeze. Aspecific recurrent wheeze was defined as dyspnea with wheeze and/or coughing for at least 3 episodes of at least 7 days, or chronic dyspnea with wheeze and/or coughing for at least 2 months. Infants were suspected to have airway malacia if they had chronic lower airway symptoms since the first weeks of life, not responding to any anti-asthma therapy. In all infants with suspected airway malacia, the diagnosis was confirmed by bronchoscopy after ILFT. Bronchoscopy was performed by a paediatric pulmonologist who was unaware of the ILFT data. Airway malacia was defined as a general or localised weakness of the trachea or bronchi, resulting in excessive narrowing of the tracheal or bronchial lumen during expiration or whenever intrathoracic pressure increases (14). Exclusion criteria were other illnesses possibly accounting for the dyspnea, such as preterm birth, cystic

fibrosis, hernia diapragmatica. Due to medical ethical reasons bronchoscopy was not performed in the wheeze group. None of the infants had received bronchodilator treatment 12 hours prior to the test.

Lung function

Lung function measurements were performed when the infants were free from acute respiratory symptoms. To prevent the infants from waking up during the measurements, they were sedated with chloral hydrate (50-75 mg/kg). Functional residual capacity (FRC_p) was measured by means of a modified whole body plethysmograph (Jaeger, Würzburg, Germany). Equipment and procedures were in accordance with guidelines, in which the FRC_p measurement is described in detail (15). Mean FRC_p of 3 to 5 technically acceptable measurements was expressed as Z score (15). Forced expiratory flow at FRC ($V'max_{FRC}$), used as a measure of airway patency, was assessed using the end-tidal rapid thoracoabdominal compression (RTC) technique (Custom-made equipment. Department for Experimental Medical Instrumentation, Erasmus University Medical Centre, Rotterdam, the Netherlands). In short, an inflatable jacket was wrapped around the infant's chest and abdomen with the arms outside the jacket. At end-tidal inspiration the jacket was inflated rapidly, resulting in a forced partial expiratory flow-volume curve. The flow at FRC was measured (figure 1a and 1b). Equipment and procedures were in accordance with guidelines, in which the RTC-technique is described in detail (16). Mean $V'max_{FRC}$ of 3 to 5 technically acceptable measurements was expressed as Z score (16).

Study design

After baseline lung function measurements, β_2-agonist was administered by metered dose inhaler (MDI) per spacer (Nebuhaler® using terbutaline, and Babyhaler® using salbutamol). Spacer and canister were shaken for at least 5 seconds. One actuation from a salbutamol or terbutaline MDI was given at a time, while holding the spacer in a horizontal position. Next, the spacer was attached vertically to the optimal fitting facemask used for ILFT. After 10 breaths (counted by 10 opening movements of the inspiration valve of the spacer) the spacer was removed. Lung function measurements were repeated after 10 minutes, using the same jacket pressure as used before bronchodilation. Measurements of FRC_p after bronchodilation could not always be repeated as some children awoke after the post-bronchodilation $V'max_{FRC}$ measurements. Heart rate (HR) and transcutaneous oxygen saturation (SaO_2) were monitored continuously by a pulse-oximeter (Nellcor, Hayward, CA, USA).

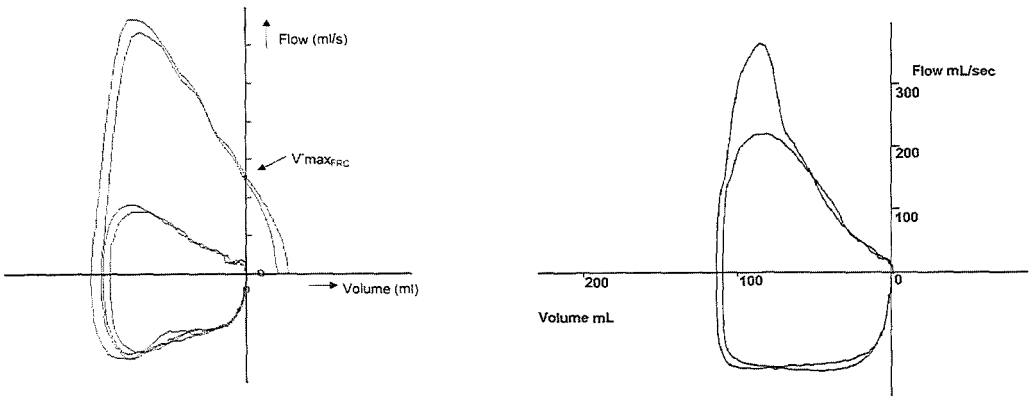

Figure 1. An example of a flow-volume loop from an infant with recurrent wheeze (a) and an infant with airway malacia (b). Note the flow limitation during tidal breathing in figure 1b.

Analysis

The effect of bronchodilation on ILFT for each infant was evaluated using a two-tailed paired Student's t-test. Subgroups were compared using the unpaired t-test. Correlation coefficients between baseline and β_2-agonist responses were obtained from linear regression analyses. The significance level was set at $p < 0.05$.

Diagnosis	Gender (M/F)	Age (weeks)	Weight (kg)	Length (cm)
Malacia	5 : 3			
Mean (range)		48 (25 – 77)	8.2 (6.0 – 11.1)	72.0 (64.0 – 82.0)
SD		21	1.6	6.7
Wheeze	14 : 5			
Mean (range)		52 (23 - 93)	9.5 (7.7 – 11.3)	75.7 (66.0 – 82.0)
SD		17	1.1	4.9
Total	19 : 8			
Mean (range)		51 (23 – 93)	9.1 (6.0 – 11.3)	74.6 (63.5 – 82.0)
SD		18	1.4	5.6

Table 1. Anthropometric data.

Results

Anthropometric data of the 27 infants are shown in table 1. The results of β_2-agonist administration on $V'max_{FRC}$ of the different groups are shown in table 2. Baseline $V'max_{FRC}$ was below reference values both groups (table 2). Baseline $V'max_{FRC}$ in the malacia group was lower than in wheeze ($p = 0.01$). Administration of β_2-agonist resulted in a reduction of the mean $V'max_{FRC}$ in both groups, but only in wheeze group this reduction was significant (figure 2). Expressed in Z scores, the mean (95% CI) change was -0.10 (-0.26 to 0.05) for the malacia group, and -0.33 (-0.55 to -0.11) for the wheeze group ($p=0.006$). When the reduction of $V'max_{FRC}$ was expressed in % of baseline, a similar pattern was observed. For the entire group mean (SD) coefficient of variation (CV) was 13.1 (7.25)%. When a significant change in $V'max_{FRC}$ was defined as being greater than twice the CV of the baseline measurement (4), only 6 out 19 infants in the wheeze group had a significant changes in $V'max_{FRC}$. Mean $V'max_{FRC}$ increased in 6 out of 27 infants after β_2-agonist administration (3 with malacia, and 3 with wheeze). The mean (range) FRC_p in Z score at baseline for the total group (n=27) was -0.20 (-1.66 to 0.54). Due to waking up after the post bronchodilator $V'max_{FRC}$ measurements, FRC_p measurements before and after bronchodilation could only be obtained in 12 infants (4 malacia, 8 wheeze). For these 12 infants the mean (95% CI) change in FRC_p in Z score after bronchodilation was –0.12 (-0.15 to 0.39) ($p=0.35$).

	Mean $V'max_{FRC}$ ml/s (range)		Mean Δ $V'max_{FRC}$ % from baseline (95% CI)	Mean $V'max_{FRC}$ Z score (range)		Mean Δ $V'max_{FRC}$ Z score (95% CI)
	Pre β2-agonist	Post β2-agonist	Post β2-agonist	Pre β2-agonist	Post β2-agonist	Post β2-agonist
Malacia (n=8)	56.2 (17 to 89)	47.5 (32 to 91)	-6.3 (-40.7 to 28.0)	-2.64 (-3.58 to –1.41)	-2.75 (-3.74 to –1.38)	- 0.10 (-0.26 to 0.05)
Wheeze (n=19)	167.1 (32 to 420)	139.8 (32 to 344)	-13.1 (-25.1 to –1.1)	-1.50 (-3.94 to 1.72)	-1.83 (-4.02 to 0.44)	-0.33 (-0.55 to -0.11)

Table 2. Effect of β_2-agonist administration on $V'max_{FRC}$, expressed in ml/s and Z scores

Due to the retrospective nature of this study β_2-agonist dosage was not standardised. Mean dosage of terbutaline (n= 24) was 333 µg (range 250-750 µg), mean dosage of salbutamol (n= 3; malacia=1, wheeze=2) was 666 µg (range 600-800 µg). There was no correlation between β_2-agonist dosage and the difference in $V'max_{FRC}$ as a percentage from baseline. Heart rate increased significantly after bronchodilation (mean increase (95% CI): 10 (6 to 14) beats/min), used as an indicator that an adequate dose was delivered into the lungs. Oxygen saturation did not change significantly after bronchodilation.

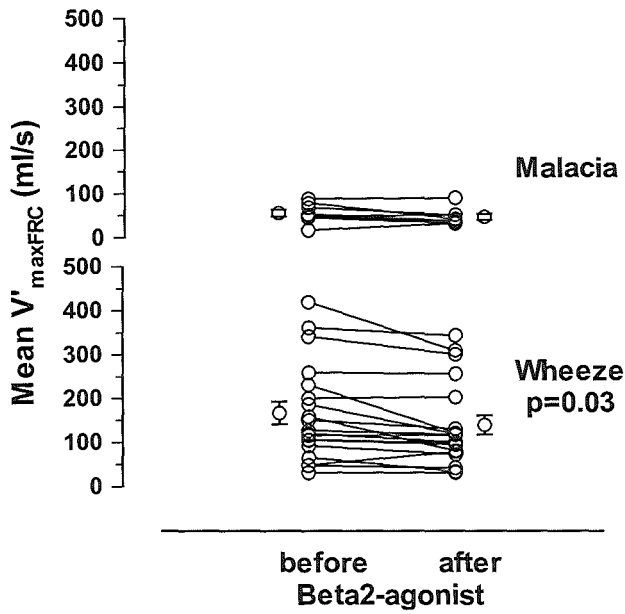

Figure 2. Individual responses of $V'max_{FRC}$ before and after β_2-agonist administration. Output organised by groups. Filled dots are mean group values with their standard error of the mean (SEM).

Discussion

We observed a reduction in mean $V'max_{FRC}$ after β_2-agonist administration in infants with wheeze and malacia. In the wheeze group this reduction was significant. Worsening of $V'max_{FRC}$ following β_2-agonists was not more likely to

occur in infants with malacia than in infants with wheeze. Therefore, we reject the hypothesis that a negative effect of β_2-agonist administration on $V'max_{FRC}$ is more pronounced in infants with airway malacia, compared to infants with wheeze.

A possible explanation for our finding could be that baseline $V'max_{FRC}$ was significantly lower in the malacia group, with flows sometimes limited to (near) tidal levels (figure 1b), and thus leaving little room for further deteriorations. Conversely, at these levels a small deterioration in lung function may be clinically more significant than a larger deterioration at higher lung function, as was seen in the wheeze group. Another explanation could be that, in malacia, forced expiration assessed with the RTC-technique is affected by dynamic compression to such an extent that a further reduction of smooth muscle tone by bronchodilation does not result in further deterioration of airway patency. Furthermore, a decrease in FRC after bronchodilation could have masked a bronchodilator response, since airway resistance is higher at lower lung volumes (17). We think this is unlikely, as we could not demonstrate a change in mean FRC_p after bronchodilation.

The significant reduction in mean $V'max_{FRC}$ in the wheeze group could be explained by the fact that the majority of infants (about 60%) with wheezing do not necessarily have reversible bronchoconstriction, but transient conditions associated with diminished airway patency (18). A reduction of smooth muscle tone by bronchodilation could make the airways more compliant, and therefore more collapsible, resulting in increased dynamic compression and reduced forced expiratory flows (12, 13). Another possible explanation for the significant reduction in mean $V'max_{FRC}$ is that the wheeze group was studied while asymptomatic when scope for improvement may be limited and scope for deterioration greater. The significant reduction in mean $V'max_{FRC}$ in the wheeze group can not be explained by a difference in β_2-agonist dosage since the mean dose was not different between groups. One could argue whether the mean decrease in $V'max_{FRC}$ in the wheeze group is clinically relevant, because when a significant change in $V'max_{FRC}$ was defined as greater than twice the CV of the baseline measurement (4) no significant changes in $V'max_{FRC}$ in either group were seen. The lack of a change in $V'max_{FRC}$ after bronchodilators in wheezy infants was also observed by others (4, 5). A possible explanation could be that, according to recommendations, $V'max_{FRC}$ after bronchodilation is assessed with the same jacket pressure as used before the administration (16). Possibly, one should assess the lowest pressure at which the highest flows are

obtained both before and after β_2-agonists administration.
Modl and co-workers (17) showed a positive effect of β_2-agonist administration on mean $V'max_{FRC}$ by means of the raised volume rapid thoracoabdominal compression (RVRTC) technique, suggesting that the RVRTC technique might be a better test for assessing forced expiratory flow. Assessing airway patency by means of the RVRTC technique is promising but has not yet proved to be beneficial over the RTC technique (19). Furthermore, RVRTC technique is not standardised since it lacks consensus (16, 20). Although the RTC technique is well accepted and standardised, several disadvantages have become apparent. First, measurement of $V'max_{FRC}$ relies on FRC not changing between forced expirations. There is abundant evidence that FRC is not stable and shifts with dynamic events such as changes in airway calibre (bronchodilation) or sleep state (21). This explains the high variability of $V'max_{FRC}$ for which coefficients of variation range from 11% to 36% (21). Second, flow limitation is difficult to ascertain, especially in healthy infants. Finally, RTC technique assesses airway function in the tidal volume range only, which reduces its sensitivity (20, 21).

This study suggests that, in clinically stable infants, mean forced expiratory flows by means of the RTC technique do not improve following inhaled bronchodilators. On the contrary, β_2-agonist administration may produce an increase in mean work of breathing per minute (22), oxygen consumption and minute ventilation possibly as the result of an increase of metabolic rate (23). Thus, β_2-agonists may not always be beneficial in infants with airway obstruction.

We conclude that mean $V'max_{FRC}$ is reduced and did not improve after inhalation of β_2-agonists in infants with malacia or wheeze. In infants with wheeze there was a significant reduction in mean $V'max_{FRC}$ after inhalation of β_2-agonists. Children with malacia were not more likely to worsen after β_2-agonists. We recommend that the response to inhaled β_2-agonists in infants with airway obstruction should always be critically evaluated.

Acknowledgement
This study was supported by an unrestricted grant from GlaxoSmithKline, the Netherlands.

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EFFICACY OF FLUTICASONE PROPIONATE ON LUNG FUNCTION AND SYMPTOMS IN WHEEZY INFANTS

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Submitted

Abstract

The role of inhaled corticosteroids in the treatment of recurrent or persistent wheeze in infancy remains unclear. We evaluated the effect of 3 months treatment with inhaled fluticasone propionate 200 µg daily (FP200) on lung function and symptom scores in wheezy infants. Moreover, we evaluated whether infants with atopy and/or eczema respond better to FP200 as compared with non-atopic infants. Forced expiratory flow ($V'max_{FRC}$) was measured at baseline and after treatment. Sixty-five infants were randomized to receive FP200 or placebo, and 62 infants (mean age 11.3 months) completed the study. Mean $V'max_{FRC}$ in Z score was significantly below normal at baseline and after treatment in both groups. The change from baseline of $V'max_{FRC}$ was not different between the two treatment arms. After 6 weeks of treatment, and not after 13 weeks, the FP200 group had a significantly higher percentage of symptom free days and a significant reduction in mean daily cough score. Separate analysis of treatment effect in infants with atopy or eczema showed no effect modification. We conclude that in wheezy infants, treatment with fluticasone did not improve lung function but did reduce respiratory symptoms after 6 weeks. Hence, fluticasone could be considered for reducing symptoms in wheezy infants.

Introduction

Recurrent episodes of wheezing are a common problem of early childhood, affecting approximately 30% of all children age 0 to 3 years (1-3). Numerous infants with wheeze are treated with inhaled corticosteroids (ICS) as it is thought that ICS reduce or reverse airway inflammation (4, 5). Moreover, it has been suggested that early introduction of ICS may have a disease-modifying effect and may prevent development of irreversible airway obstruction (5, 6). However, data from studies determining the effectiveness of inhaled steroids in infants with recurrent wheezing are equivocal (7-16). The anti-inflammatory properties of fluticasone propionate (FP) are known to be at least twice as potent as beclomethasone dipropionate or budesonide (17). Three studies evaluated the effect of FP on symptom scores in wheezy infants (13, 14, 16). To our knowledge, no study evaluated the effect of FP in wheezy infants using objective end points. As it is known that only a minority of all wheezing infants has asthma (18), it has been suggested that atopic infants are more likely to respond to ICS treatment as compared with non-atopic infants (14, 19).
We aimed to evaluate the effect of fluticasone propionate on lung function and symptom scores in infants with recurrent or persistent wheeze. The second aim was to evaluate the treatment effect in subgroups of infants with atopy or eczema.

Methods

Patients

Inclusion criteria were age 4 - 24 months, 3 or more reported wheezing episodes, or persistent wheezing for more than 2 months. Exclusion criteria were lung disease other than asthma, gastro-esophageal reflux, premature birth, and corticosteroid treatment in the month before the start of study. The study was approved by the medical ethical committees of all participating hospitals. All parents gave informed consent.

Study design

We performed a randomized, double blind, placebo controlled study, with a treatment period of 3 months (Figure 1). During the first visit a physical examination was performed and a modified ISAAC questionnaire (20) completed. At the second visit a lung function test was performed. Infants were then stratified for baseline lung function and randomized to receive fluticasone propionate 200 µg daily (FP200) or placebo, ratio 2 :1. To minimize seasonal

influences, infants were randomized in blocks of three (2 FP200 : 1 placebo). Subjects were allowed to use salbutamol as needed (Ventolin 100 µg). At the fourth visit, lung function measurements were repeated and study medication was stopped.

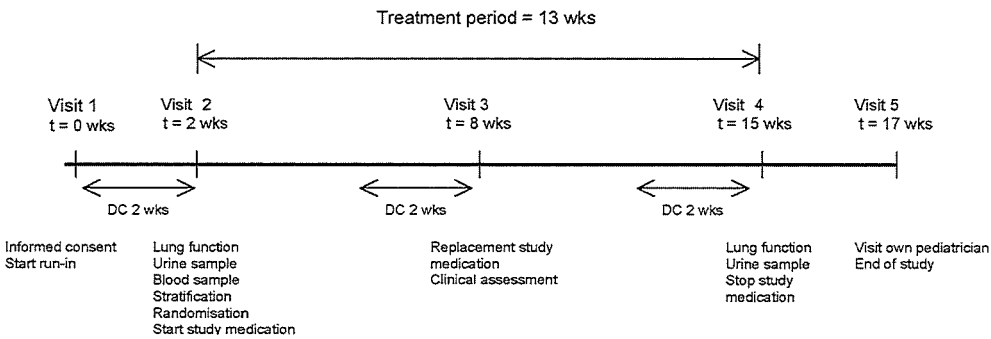

Figure 1. Study design. DC 2 wks: diary card for symptoms, scored in the two weeks prior to the next visit.

Lung function measurements

Infants were sedated with chloral hydrate. We measured airway resistance using the interrupter technique (R_{int}), functional residual capacity (FRC_p) by means of a whole body plethysmograph, and forced expiratory flow at FRC ($V'max_{FRC}$) using the end-tidal rapid thoracoabdominal compression (RTC) technique. Equipment and procedures were in accordance with guidelines (21-23). Mean $V'max_{FRC}$ and mean FRC_p were expressed as Z score (22, 24).

Symptom scores

Parents recorded symptoms in the 2 weeks prior to visit 2, 3 and 4. The diary card asked for daytime and nocturnal symptoms of dyspnea, cough and wheeze on a scale from 0 (no symptoms) to 3 (severe symptoms), the number of salbutamol puffs and cooperation of the child while giving the medication.

Blood samples

Capillary blood was obtained for determination of total IgE and specific IgE (house dust mite/cat/dog, grass/birch pollen, and cow's milk/hen's egg mixes).

Statistics

Power calculations for the primary endpoint, $V'max_{FRC}$ in Z score, led to a study size of 60 infants. Secondary endpoints were the mean percentage of symptom free days per diary card period, the mean daily total scores of wheeze, dyspnea and cough and the mean daily number of salbutamol doses taken. Diary cards with less than 50% of days scored properly were excluded. Other secondary endpoints were: FRC_p and R_{int}. Changes from baseline of lung function parameters were compared using analysis of covariance with adjustment for baseline values. Within-group changes from baseline were evaluated using the paired T-test. Evaluation of the various diary card data for the 2 diary card periods during treatment was done with repeated measurements ANOVA, with adjustment for the outcome at the baseline run-in period. Separate analysis of treatment effect was performed in subgroups of infants with atopy (personal or parental history of asthma, eczema or hay fever), or infants with eczema. Additionally, exploration of baseline patient characteristics regarding the change of $V'max_{FRC}$ was performed using univariate analyses. A p-value ≤ 0.05 was considered significant.

	Total group n=62	FP200 group n=40	Placebo group n=22
Age at baseline measurement (months)	11.3 (4.4)	11.0 (4.5)	12.0 (4.1)
Height (cm)	75.2 (6.3)	74.1 (6.4)	77.2 (5.8)
Weight (kg)	9.8 (1.8)	9.5 (1.8)	10.2 (1.7)
Boys	40 (65%)	27 (68%)	13 (59%)
Atopy	46 (74%)	28 (70%)	18 (82%)
Eczema	22 (35%)	13 (33%)	9 (41%)
Prenatal passive smoking	19 (31%)	11 (28%)	8 (36%)
Environmental tobacco smoke exposure	12 (19%)	8 (20%)	4 (18%)
Total IgE (IU/ml)	5.4 (0.3 to 313.0)	3.8 (0.3 to 313.0)	6.4 (0.4 to 179.0)
Elevated total IgE	28 (45%)	15 (38%)	13 (59%)
Positive specific IgE	14 (23%)	10 (25%)	4 (20%)

Table 1. Anthropometric data of the total group and of the subgroups treated with fluticasone propionate 200 µg daily (FP200) or with placebo. Data presented are mean (SD), median (range) or total numbers with percentages. Atopy was defined as parental or personal history of asthma, eczema or hay fever.

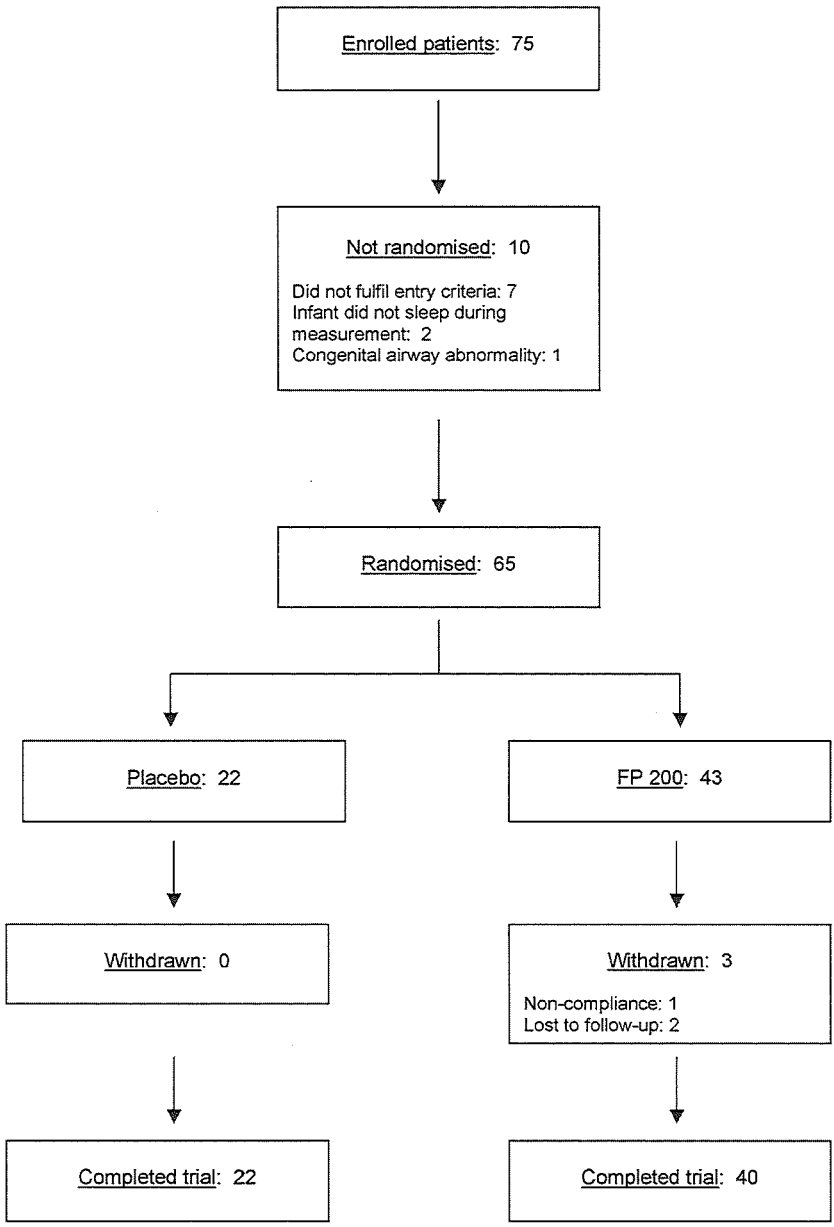

Figure 2. Patient flow through the study

Results

Seventy-five infants were enrolled into the trial. Sixty-five infants were randomized and 62 infants completed the study (Figure 2). Anthropometric data of the total group, and of the 2 subgroups are shown in table 1. The mean (SD) treatment duration for the whole group was 13.2 (1.3) weeks and did not differ between the two study arms. The results of the lung function measurements are shown in table 2. For the whole group, and for the two treatment groups separately, mean (SD) $V'max_{FRC}$ in Z score was significantly below the mean normal level (Z score=0) both at baseline and after the treatment period ($p<0.001$) (Table 2, figure 3). The change from baseline of $V'max_{FRC}$ in Z score did not significantly differ between the FP200 and placebo group (Mean (95% CI) adjusted difference 0.2 (-0.3 to 0.6) ($p=0.46$)). During the treatment period, both groups showed no significant change in mean $V'max_{FRC}$ in Z score (Mean (95% CI) change 0.1 (-0.2 to 0.4) and 0.1 (-0.3 to 0.5) for the FP200 group and the placebo group, respectively).

	Fluticasone propionate 200 mg daily			Placebo		
	Baseline	After 13 weeks	Change from baseline	Baseline	After 13 weeks	Change from baseline
$V'max_{FRC}$ (ml/s)	148.9 (76.0)	184.9 (71.0)	36.0 (15.8 to 56.2) *	144.9 (69.9)	180.5 (96.5)	35.6 (5.7 to 65.5)
$V'max_{FRC}$ (Z score)	-1.5 (1.1)	-1.4 (1.0)	0.1 (-0.2 to 0.4)	-1.9 (1.0)	-1.8 (1.0)	0.1 (-0.3 to 0.5)
FRC_p (ml/kg)	23.6 (3.6)	24.0 (3.8)	0.4 (-1.0 to 1.8)	24.2 (4.4)	23.5 (4.0)	-0.7 (-2.5 to 1.2)
FRC_p (Z score)	-0.8 (1.1)	-0.7 (1.0)	0.1 (-0.4 to 0.5)	-0.7 (1.2)	-0.8 (1.1)	-0.2 (-0.7 to 0.3)
R_{int} (kPa/L/s)	3.33 (1.17)	2.99 (0.73)	-0.35 (-0.77 to 0.07)	3.24 (1.03)	2.77 (0.78)	-0.48 (-0.95 to -0.01)

Table 2. Mean (SD) lung function data before and after 13 weeks treatment with either placebo or fluticasone propionate 200 mg daily. $V'max_{FRC}$: Forced expiratory flow at FRC. FRC_p: Functional residual capacity. R_{int}: Resistance measured by means of the interrupter technique.

At baseline, the mean percentage of symptom free days was similar for both the placebo and the FP200 group (Figure 4). In both treatment groups, there was a significant increase in percentage of symptom free days from baseline after 6 and 13 weeks of treatment. After 6 weeks of treatment, the mean percentage of symptom free days adjusted for baseline was significantly higher in the FP200

group as compared with the placebo group (Mean (95% CI) difference: 23% (3 to 43) (p=0.02)). After 13 weeks of treatment, the mean percentage of symptom free days was similar in both groups (Mean (95% CI) adjusted difference: 12% (-11 to 34) (p=0.30)). At baseline, the mean daily use of salbutamol was similar for both groups and the changes from baseline were not significantly different within or between groups.

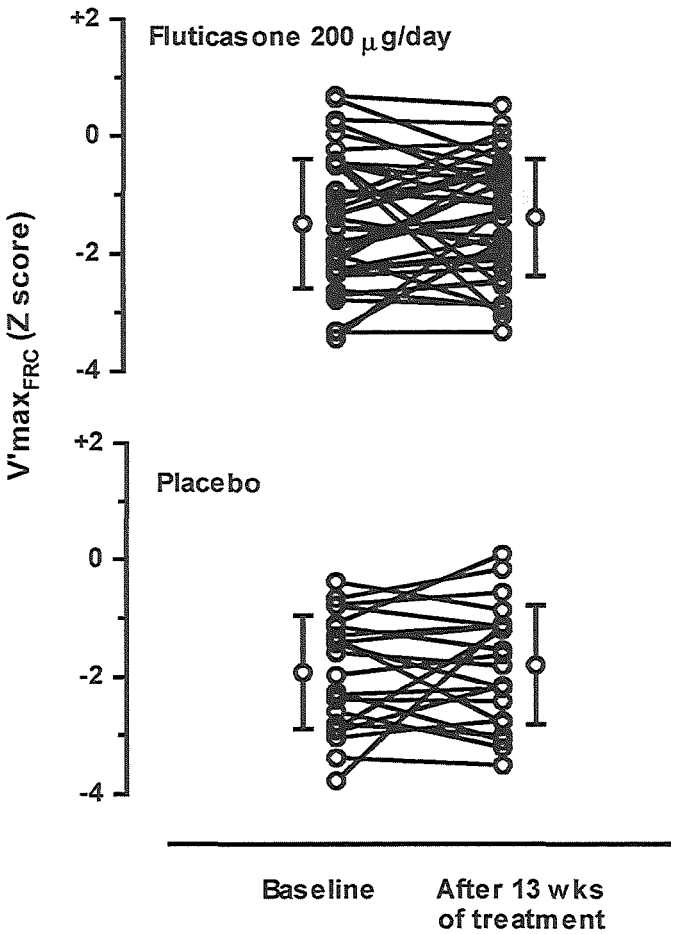

Figure 3. Individual and mean (SD) V'max$_{FRC}$ data at baseline and after 13 weeks of treatment with either placebo or fluticasone propionate 200 mg daily.

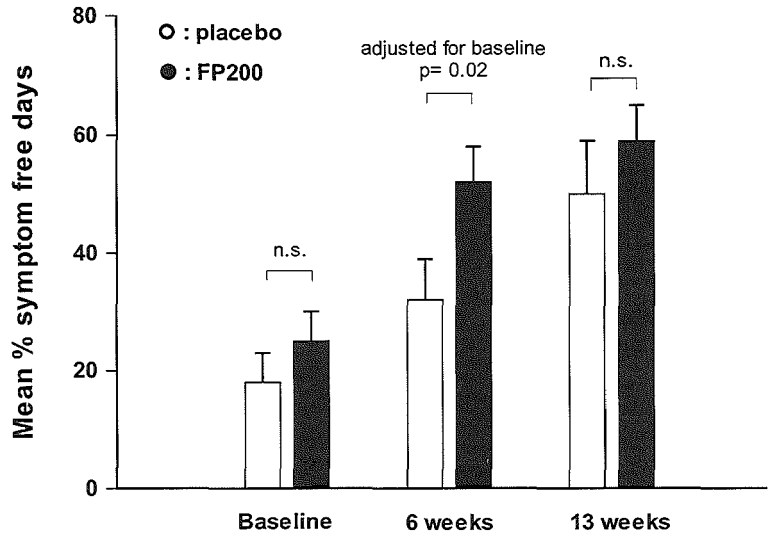

Figure 4. Mean (SEM) percentage of symptom free days at baseline and after 6 and 13 weeks of treatment with either placebo or fluticasone propionate 200 mg daily (FP200). After 6 weeks of treatment, the mean percentage of symptom free days was significantly higher in the FP200 group as compared with the placebo group (Mean (95% CI) difference adjusted for baseline: 23% (3 to 43) (p=0.02)).

When the mean daily total scores (daytime plus nocturnal scores) of wheeze, dyspnea and cough were analyzed separately, there was a significant reduction from baseline during the complete treatment period for all three parameters in the FP200 group (Table 3). In the placebo group there was only a significant reduction from baseline in mean daily cough score at 13 weeks. However, when these reductions from baseline were compared between the two treatment groups, only after 6 weeks of treatment the mean daily cough score was significantly lower in the FP200 group as compared with the placebo group (Mean (95% CI) adjusted difference: 0.7 (0.1 to 1.4)(p=0.03). At baseline, the mean score for nocturnal disturbance due to respiratory symptoms and the degree of the infant's cooperation while administering the drug were similar for both groups and the changes from baseline were not significantly different within or between groups. For both treatment groups the reported degree of cooperation was good (Mean score 1; indicating quiet breathing between 10 and 20 seconds per puff).

	FP200			Placebo		
	Wheeze	Dyspnea	Cough	Wheeze	Dyspnea	Cough
Baseline	1.1 (0.2)	1.2 (0.2)	1.8 (0.2)	0.7 (0.2)	1.0 (0.2)	1.7 (0.2)
6 wks	0.6 (0.2)*	0.6 (0.2)*	0.9 (0.2)*	0.7 (0.3)	0.9 (0.3)	1.6 (0.3)
13 wks	0.6 (0.2)*	0.6 (0.2)*	0.8 (0.2)*	0.5 (0.2)	0.6 (0.2)	1.1 (0.2)#

Table 3. Mean (SEM) daily symptomscores at baseline, after 6 weeks and after 13 weeks of treatment with fluticasone propionate 200 mg daily (FP200) or placebo. *: significant change from baseline ($p<0.02$). #: significant change from baseline ($p=0.05$). Only after 6 weeks of treatment the mean daily cough score adjusted for baseline was significantly lower in the FP200 group as compared with the placebo group (Mean (95% CI) difference: 0.7 (0.1 to 1.4)($p=0.03$).

When the change from baseline of FRC_p and R_{int} was compared between treatment groups, the adjusted differences of means were not significant ($p=0.65$ and $p=0.38$, respectively). In the placebo group the R_{int} showed a significant decrease, whereas in the FP200 group the decrease was not significant. For the whole group there was a significant decrease of R_{int} during the study ($p=0.01$). This is probably the result of increasing age as R_{int} correlated significantly with age ($r = -0.34$, $p=0.007$). After adjustment for age, there was no significant difference anymore in R_{int} before and after treatment in both groups. Tidal breathing parameters (tidal volume, breathing frequency and minute ventilation per kilogram body weight) were similar for both treatment groups at baseline, and the changes from baseline were not significantly different within or between groups.

Separate analysis of treatment effect of $V'max_{FRC}$ (Z score) was performed in subgroups of infants with atopy (defined as personal or parental history of asthma, eczema or hay fever), and in infants with eczema. In these subgroups there was no evidence of a significant treatment effect ($p= 0.77$ and $p=0.79$, respectively). In an exploratory analysis it was found that the presence of elevated total IgE, specific IgE, smoking during pregnancy or and postnatal environmental tobacco smoke exposure did not affect the results.
During treatment, infants in both study arms showed a significant increase in height (Mean (95% CI) increase of 3.4 cm (2.9 to 3.9) and 4.1 cm (3.4 to 4.7) in the placebo and FP200 group, respectively). Canisters were weighed to check compliance and there was no difference in weight reduction between the first

6 weeks and last 7 weeks in either study arm, nor did we find a difference between groups. Non-serious adverse events were not different between groups, with no oral candidiasis. Three infants experienced a serious adverse event of which none was judged to be related to study medication. In one infant a delayed psychomotor development was diagnosed during the study (in FP200 group), and 2 infants experienced a febrile seizure requiring hospitalization (1 FP200, 1 placebo).

Discussion

Infants with recurrent or chronic wheeze did not show improved lung function from a 3 months treatment with fluticasone 200 µg daily, inhaled via a Babyhaler. We therefore reject the hypothesis that FP improves lung function in infants with recurrent or persistent wheezing. However, after 6 weeks of treatment, the infants treated with FP200 had a significant improvement in symptom free days and a significant reduction in mean daily cough score, as compared with placebo. After 13 weeks of treatment, these findings were not different between the study arms. Treatment effect was not modified by the presence of atopy or eczema.

Several studies evaluated the role of inhaled steroids in the treatment of wheezy infants (7-16, 25). Only 3 studies used objective end points, such as lung function (11, 12, 25). Kraemer and coworkers (12) studied the combined efficacy of beclomethason dipropionate (BDP) and salbutamol, which makes it difficult to estimate the benefit from steroid treatment alone. Maayan and coworkers (25) studied the efficacy of 2 weeks treatment with ICS in 9 wheezy infants. From this study duration and small sample size, no conclusions can be drawn. Stick and coworkers (11) evaluated the efficacy of 8 weeks treatment with BDP in 38 infants with recurrent wheezing. They found that symptoms improved for both the placebo and the ICS group, whereas $V'max_{FRC}$ improved significantly in the placebo group, but not in the ICS group (11). Only two studies evaluated the efficacy of FP using subjective outcome measures in young children (13) (14). To our knowledge, no study evaluated the efficacy of treatment with FP in infants with wheeze using objective parameters, next to symptom scores. This makes our study the first large randomized controlled trial on the effect of FP on objective outcome measures in infants.

Three studies evaluated the effect of fluticasone propionate in wheezy infants

(13, 14, 16). They found a significant improvement from baseline in symptom scores, and a lower number of patients with at least one exacerbation during treatment in the FP group as compared with placebo. We only found an improvement in symptom scores after 6 weeks of treatment. An explanation could be that the children in the study by Bisgaard and coworkers were slightly older, with a mean age of 28 months (13). One could speculate that a larger proportion of children above 2 years of age has wheezing related to asthma. Consequently, treatment with ICS could be more effective. In the studies by Chavasse and coworkers (14) and Teper and coworkers (16) only wheezy infants with a history of atopy were included. These infants are known to be at high risk for developing asthma, and therefore inhaled steroids may be more effective. In our study, all infants with recurrent or persistent wheeze were included, irrespective of atopy. After 6 weeks of treatment, but not after 13 weeks, there was a significant improvement in symptom scores in the FP200 group. An explanation could be that the reduction in symptoms at 6 weeks in the FP200 group led to a decrease in compliance. However, canisters were weighed to check compliance and we found no difference in weight reduction between the first 6 weeks and last 7 weeks of treatment in the FP200 group, nor did we find a difference between groups. Therefore, we don't think differences in compliance explain our results.

Separate analysis of treatment effect in subgroups of infants with atopy or eczema in our study showed no effect modification. This is in contrast with a study by Chavasse and coworkers, showing improvement of clinical symptoms in response to FP in a group of atopic wheezy infants (14). In addition, Roorda and coworkers showed that preschool children (aged 12-47 months) with recurrent asthma symptoms showed the greatest response to FP treatment if they had frequent symptoms, a family history of asthma, or both (19). Our study does not confirm that atopic infants are more likely to respond to ICS treatment than non-atopic infants.

There are several possible explanations for the lack of a clear effect of FP200 treatment on lung function in our study. First, the majority of infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life (18). Infants who have respiratory illnesses with wheezing in the first year of life have lower levels of lung function before any lower respiratory illness develops, than infants who do not have illnesses with wheezing (26). This suggests that small airways predispose many infants to wheezing in association with com-

mon viral infections (18). The effect of ICS in non-asthmatic viral wheeze is uncertain. Another explanation could be that our lung function measurements were insensitive to detect ICS effects. However, $V'max_{FRC}$ has proven to be a sensitive parameter for peripheral airway patency in several physiologic, clinical and epidemiological investigations (24) and has been used to study airway responsiveness, diseases and the impact of treatment strategies in infants (24, 27-30). In addition, none of the other lung function parameters that we studied showed a significant improvement. On the other hand, lung function measurements are known to correlate poorly with symptoms as scored by the parent in wheezy infants (31). It can be argued that a larger effect might be seen in infants with more severe respiratory symptoms. We think that this is unlikely as the baseline values for $V'max_{FRC}$ were significantly below zero for both groups. In addition, at baseline the percentage of symptom free days was only about 20% for the whole group, suggesting that there was room for improvement. Another possible explanation for the lack of response in $V'max_{FRC}$ to FP200 could be an inadequate steroid dose. We consider this unlikely as Bisgaard and coworkers showed that even 100 µg FP daily was effective in reducing asthma symptoms in a large group of young children (13). One might argue that in infants, inadequate drug delivery to the airways explains a lack of response to inhaled medication. However, 2 studies showed a reduction in symptoms after FP treatment in infants (13) (14), suggesting that the Babyhaler with MDI is able to deliver a clinically effective dose of aerosol in infants. Moreover, urinary cortisol measurements indicate that approximately 8% of the nominal steroid dose is inhaled from the Babyhaler (32). In our study, inhalation technique was instructed according to recent recommendations (33) and was checked regularly. In both study arms the reported cooperation was good. Since there was an effect on symptom scores in the FP200 group, we believe that inadequate delivery is not a likely explanation for the lack of response in lung function to FP200 in our study. Finally, treatment for 3 months could be too short to show an effect. However, a treatment effect is established after 6 to 8 weeks (7), and a treatment period of 12 weeks was sufficient to show a reduction in symptom scores (13) (14). We therefore think that 3 months is an adequate treatment period.

We conclude that in infants with recurrent or persistent wheeze, FP200 treatment did not improve lung function. However, FP200 treatment reduces symptoms and is safe in infants with wheeze. Our study suggests that a treatment effect should be present after 6 weeks of treatment and that further improvement in respiratory symptoms is not likely after 13 weeks of treatment.

Acknowledgement:
This study was supported by an unrestricted grant from GlaxoSmithKline, the Netherlands.

Thanks are due to the parents and the children, Wim Holland (Department of Experimental Medical Instrumentation, Erasmus MC, Rotterdam) and all participating pediatricians of the AIR-study group: Medical Center Rijnmond Zuid, Rotterdam: Dr. F.J. Smit. Amphia Hospital, Breda: Dr. A.A.P.H. Vaessen-Verberne. A. Schweitzer Hospital, Dordrecht: Dr. R. Schornagel. R. de Graaf Gasthuis, Delft: Dr. P.J. van der Straaten. Groene Hart Hospital, Gouda: Dr. F.G.A. Versteegh. Beatrix Hospital, Gorinchem : Dr. R.M. Colombijn. Sint Franciscus Gasthuis: Dr. M.C.W. Jacobs. Sophia Children's Hospital: Dr. M.J. Affourtit, Dr. W.W. Abels.

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Worsening of forced expiratory flows in infants with CLD in the first year of life: A more favorable outcome after HFO ventilation

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Am J Resp Crit Care Med 2002;166:1539-1543

Abstract

Little is known about the development of forced expiratory flow, a measure of airway patency, in infants with chronic lung disease (CLD). In a follow-up study we evaluated forced expiratory flow ($V'max_{FRC}$), in very low birth weight (VLBW) infants with CLD, treated with high-frequency oscillation ventilation (HFOV) or conventional mechanical ventilation (CMV). In 36 infants with CLD, $V'max_{FRC}$ was evaluated at 6 and/or 12 months corrected age, and the relationship between perinatal factors and lung function was studied. Mean (SD) birth weight and gestational age were 837 (152) grams and 26.8 (1.7) weeks, respectively. At 6 and 12 months mean $V'max_{FRC}$ was significantly below normal. Between 6 and 12 months there was a mean (95% CI) reduction in $V'max_{FRC}$ (Z score) of 0.5 (0.2 to 0.7)($p<0.001$). At 12 months the mean $V'max_{FRC}$ (Z score) was higher for children initially treated with HFOV (n=15), as compared to children treated with CMV (n=16): mean (95% CI) difference was 0.6 (0.2 to 1.0)(p=0.008). We conclude that VLBW infants with CLD have decreased forced expiratory flows that worsen during the first year of life. Initial treatment with HFOV was associated with a more favorable outcome of forced expiratory flows at 12 months corrected age.

Introduction

Chronic lung disease (CLD) is a common sequel of mechanical ventilation and oxygen therapy in prematurely born infants (1). Despite advances in prenatal and neonatal care, including antenatal and postnatal steroids, surfactant treatment, high-frequency oscillation ventilation (HFOV), CLD is still one of the major complications in mechanically ventilated premature infants (2). The overall incidence of CLD has remained high as a result of the increased survival of extremely premature infants, who are most likely to develop CLD (2). Long-term studies show that survivors of CLD have abnormal pulmonary function tests at school age (3, 4), whereas infants who received initial HFOV showed normal lung function at school age (5). Only a few studies evaluated lung function during the first years of life in children with CLD. In young children with CLD, lung function parameters, such as functional residual capacity, compliance, resistance and conductance, show a gradual improvement towards the normal range during the first three years of life (6-8). Nevertheless, forced expiratory flows, used as a measure of airway patency, are known to be decreased during the first two years of life (6, 8, 9). Due to advances in prenatal and neonatal care, results obtained in the past may not be valid for infants who develop CLD nowadays. There are no recent studies that evaluated forced expiratory flows during the first year of life in very low birth weight (VLBW) infants with CLD, in the era of surfactant therapy and HFOV.
Therefore, we aimed to evaluate forced expiratory flows at 6 and 12 months corrected age, in a group of VLBW infants with CLD. Furthermore, we studied the relationship between lung function and perinatal patient characteristics.

Methods

Subjects

A follow-up study was conducted in neonates who developed CLD, born between January 1998 and September 1999. All infants were born in, or immediately after birth transferred to the Neonatal Intensive Care Unit (NICU) of the Sophia Children's Hospital. The inclusion criteria were: (a) VLBW: birth weight ≤1250 g, (b) need for mechanical ventilation from day 1 for at least 7 days, (c) need for continuous supplemental oxygen at 28 days and/or at 36 weeks gestational age, (d) chest radiogram at 1 month of age typical for CLD. Exclusion criteria were major congenital anomalies, meconium aspiration, or suspected hypoplasia of the lungs. Artificial ventilation in the NICU was administered by

conventional mechanical ventilation (CMV) or high-frequency oscillation ventilation (HFOV). Initial ventilation strategy was not randomized in our study. Preferably, initial HFOV was started in the youngest and smallest infants. This was not always feasible due to the limited availability of HFOV-equipment, and hence, initial ventilation strategy was partly determined by chance. When infants developed hyaline membrane disease (HMD), surfactant (Survanta® 100mg/kg/dose) was administered. Neonates with severe HMD received additional doses. When infants developed a persistent need for artificial ventilation, treatment also included fluid restriction and diuretics. In order to wean them off the ventilator, most infants were treated with dexamethasone, administered in a 3-week course starting with a dose of 0.5 mg/kg/day and gradually tapering down. All infants were age corrected to a gestational age (GA) of 40 weeks. The study was approved by the medical ethical committee of the Erasmus University Medical Center. All parents gave informed consent.

Lung function

Lung function measurements were performed at 6 and 12 months corrected age, when the infants were free from acute respiratory symptoms. To prevent the infants from waking up during the measurements, they were sedated with choral hydrate (50-75 mg/kg). Functional residual capacity (FRC_p) was measured by means of a modified whole body plethysmograph (Jaeger, Würzburg, Germany). Equipment and procedures were in accordance with recently published guidelines, in which the FRC_p-measurement is described in detail (10). Mean FRC_p of 3 to 5 technically acceptable measurements was expressed as Z score (10). Maximal flow at FRC ($V'max_{FRC}$), used as a measure of airway patency, was assessed using the end-tidal rapid thoracoabdominal compression (RTC) technique (Custom-made equipment. Department for Experimental Medical Instrumentation, Erasmus University Medical Center, Rotterdam, the Netherlands). Equipment and procedures were in accordance with recently published guidelines, in which the RTC- technique is described in detail (11). Mean $V'max_{FRC}$ of 3 to 5 technically acceptable measurements was expressed as Z score according to Sly et al (11) and Tepper et al(12).

Analysis

Lung function at the first and second measurement was compared using mixed-model ANOVA (SAS, PROC MIXED). Between the groups initially treated with HFOV or CMV, lung function and anthropometric data were compared using independent-samples T tests. Comparison of percentages was done using Fisher's exact test. Where applicable, the difference in lung function was eva-

luated using paired Student's T-test. The influence of various perinatal variables on level of lung function was evaluated by multiple regression analyses. The significance level was set at $p < 0.05$.

Results

A cohort of 36 Caucasian infants was enrolled. At 6 months lung function was measured in 28 infants, at 12 months in 31 infants. In 23 infants lung function was measured both at 6 and 12 months corrected age. Reasons for not completing both measurements were failure to sleep during the procedure (n=6), airway infections (n=5), and loss to follow-up (n=2). Anthropometric data of the total cohort of 36 infants, and of the subgroups of 28 infants measured at 6 months and 31 infants measured at 12 months, are shown in table 1.
The first and second lung function measurements were performed at a mean (SD) corrected age of 6.2 (0.9) and 12.6 (1.1) months, respectively. The results of the FRC_p and the $V'max_{FRC}$ measurements are shown in table 2. Mean (SEM) FRC_p in Z score at the first and second measurement was -1.2 (0.3) and -0.6 (0.2), respectively. Mean (SEM) $V'max_{FRC}$ in Z score was significantly below zero (normal value) at the first and second measurement: -1.7 (0.1) and −2.2 (0.1) respectively (table 2, figure 1). Between the two measurements there was a mean (95% CI) change of $V'max_{FRC}$ in Z score of -0.5 (-0.7 to -0.2) ($p<0.001$). When $V'max_{FRC}$ in Z score was calculated using normative data by Tepper et al (12), similar results were seen: the mean (SEM) $V'max_{FRC}$ (Z score) at the first and second measurement was: -1.6 (0.1) and −2..0 (0.1), respectively (mean (95% CI) change of $V'max_{FRC}$ in Z score of −0.4 (-0.7 to -0.1) ($p=0.006$).

At 12 months mean (SEM) $V'max_{FRC}$ in Z score was better in the group who received initial HFOV (n=15) as compared to the group who initially received CMV (n=16): -1.9 (0.2) and −2.5 (0.1), respectively (mean (95% CI) difference: 0.6 (0.2 to 1.0), $p=0.008$) (table 3). The distributions of perinatal factors did not differ between these two groups, except for birth weight (g) and requirement of surfactant therapy (table 4). After allowing for the potential confounders (days on ventilation, gestational age and birth weight) using multiple regression analyses, this difference remained significant ($p=0.038$). However, when both ventilation groups were compared with adjustment for number of surfactant dosages, the difference in mean $V'max_{FRC}$ (Z score) at 12 months lost significance ($p=0.085$).

	Total group n=36	Infants measured at 6 months (n=28)	Infants measured at 12 months (n=31)
Gestational age (wk)	26.8 (1.7)	26.9 (1.7)	26.9 (1.7)
Birth weight (g)	837 (152)	826 (156)	852 (156)
Birth weight (Z score)*	-1.2 (1.3)	-1.4 (1.1)	-1.2 (1.4)
Males	22	18	19
Maternal steroids	28	22	24
Tocolyses	24	19	21
PROM	7	7	5
PDA	27	19	24
Surfactant treated newborns	29	23	24
Dexamethasone treated newborns	32	25	27
Duration dexamethasone treatment (days)	23 (15)	21 (10)	25 (16)
Initial HFOV	18	15	15
Duration of ventilation (days)	27 (13)	25 (10)	27 (14)
Duration of oxygen dependence (days)	151 (161)	150 (174)	166 (169)
Oxygen dependence at 28 days	35	27	30
Oxygen dependence at GA 36 weeks	30	22	26

Table 1. Anthropometric data. Data given are number of infants or mean (SD). Shown are the total group, and the subgroups of infants measured at 6 months, and measured at 12 months corrected age. Twenty-three infants completed both measurements. *: Reference values by Usher and McLean (22). PROM: premature rupture of membranes. PDA: persistent ductus arteriosus. HFOV: high-frequency oscillation ventilation. GA: gestational age.

	Measurement 1 (n=28) Mean ± SEM	Measurement 2 (n=31) Mean ± SEM	Mean difference (95% CI)
FRC_p (ml/kg)	23.6 ± 1.3	25.5 ± 1.0	1.9 (-1.3 to 5.0)
FRC_p (Z score)*	-1.2 ± 0.3	-0.6 ± 0.2	0.6 (-0.2 to 1.4)
$V'max_{FRC}$ (ml/s)	70.3 ± 9.4	119.0 ± 9.0	48.7 (26.9 to 72.4)‡
$V'max_{FRC}$ (Z score)†	-1.7 ± 0.1	-2.2 ± 0.1	-0.5 (-0.7 to –0.2)‡

Table 2. Lung function during first year of life in infants with CLD. Results of lung function measurements in infants with CLD during the first year of life. At measurement 1 and 2, the mean (SD) corrected age was 6.2 (0.9) and 12.6 (1.1) months, respectively. FRC_p: functional residual capacity. $V'max_{FRC}$: forced expiratory flow at FRC. *: Reference equation by Stocks et al.(10). †: Reference equation by Sly et al(11). ‡: $p<0.001$.

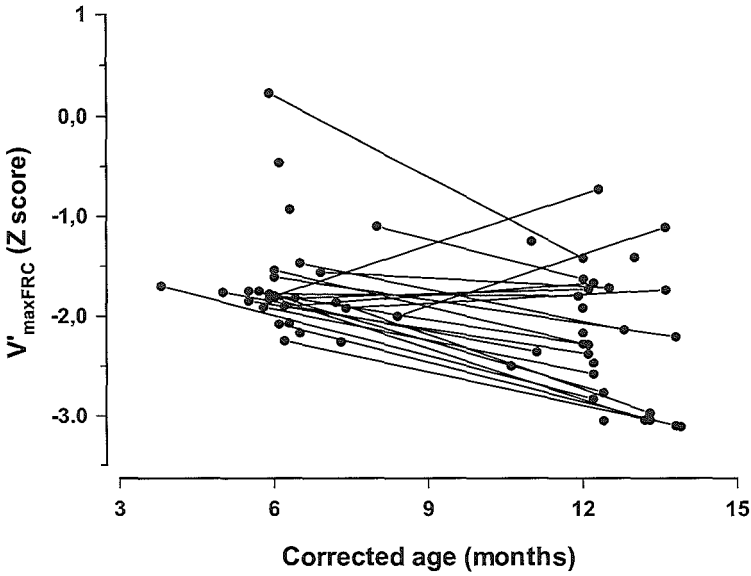

Figure 1. Lung function data of 36 infants with CLD. Mean forced expiratory flow at FRC ($V'max_{FRC}$) is expressed in Z score according to Sly et al (11). The first (n=28) and second (n=31) measurement were done at a mean (SD) corrected age of 6.2 (0.9) and 12.6 (1.1) months, respectively. Twenty-three infants completed both measurements (connected datapoints).

	HFOV (n=15)	CMV (n=16)	Mean difference (95% CI)
FRC_p (ml/kg)	25.5 ± 1.3	25.5 ± 1.4	n.s.
FRC_p (Z score)*	-0.6 ± 0.3	-0.6 ± 0.4	n.s.
$V'max_{FRC}$ (ml/s)	148.1 ± 11.9	89.7 ± 11.3	58.5 (24.9 to 92.0)‡
$V'max_{FRC}$ (Z score)†	-1.9 ± 0.2	-2.5 ± 0.1	0.6 (0.2 to 1.0)§

Table 3. Lung function at 12 months corrected age, after initial HFOV or CMV. Results of lung function measurements (mean (SEM) or (95% confidence interval)) in infants with CLD, treated with conventional mechanical ventilation (CMV), or treated with first intention high-frequency oscillation ventilation (HFOV). FRC_p: functional residual capacity. $V'max_{FRC}$: forced expiratory flow at FRC.
*: Reference equation by Stocks et al.(10). †: Reference equation by Sly et al.(11) ‡: p=0.001. §: p=0.008

	Initial HFOV n=15	Initial CMV n=16
Gestational age (wk)	26.5 (1.7)	27.2 (1.8)
Birth weight (g)	778 (135) †	921 (146) †
Birth weight (Z score) *	-1.5 (1.6)	-0.9 (1.1)
Males	12	7
Maternal steroids	14	10
Tocolyses	12	9
PROM	3	2
PDA	10	14
Surfactant treated newborns	9 ‡	15 ‡
Number of surfactant doses	1 (0-2) §	2 (0-4) §
Dexamethasone treated newborns	14	13
Duration dexamethasone treatment (days)	24 (11)	25 (20)
Duration of ventilation (days)	28 (10)	26 (17)
Duration of oxygen dependence (days)	127 (128)	202 (197)
Oxygen dependence at 28 days	14	16
Oxygen dependence at GA 36 weeks	13	13

Table 4. Anthropometric data of the infants measured at 12 months corrected age, subgrouped by initial ventilation treatment. Data given are number of infants, mean (SD) or median (range). Shown are the anthropometric data of the 31 infants who's lung function was measured at 12 months corrected age, subgrouped by initial ventilation treatment. *: Reference values by Usher and McLean (22). †: p=0.009. ‡: p=0.037. §: p=0.002. HFOV: high-frequency oscillation ventilation. CMV: conventional mechanical ventilation. PROM: premature rupture of membranes. PDA: persistent ductus arteriosus. GA: gestational age.

Similar results were seen within the subgroup of 23 infants who completed both measurements. To study the difference between 6 and 12 months precisely, individual mean $V'max_{FRC}$ values were inter- or extrapolated linearly to values at exactly 6 and 12 months corrected age. At 6 and 12 months the mean (SEM) of these adjusted $V'max_{FRC}$ (Z score) values were: -1.7 (0.1) and -2.1 (0.1), respectively (mean (95% CI) change: -0.4 (-0.7 to -0.1), p=0.006). At 12 months the mean (SEM) of the adjusted $V'max_{FRC}$ in Z score was better in the group who received initial HFOV (n=12) as compared to the group who received CMV (n=11): -1.9 (0.2) and −2.4 (0.1), respectively (mean (95% CI) difference: 0.6 (0.1 to 1.0), p=0.014) (Figure 2).

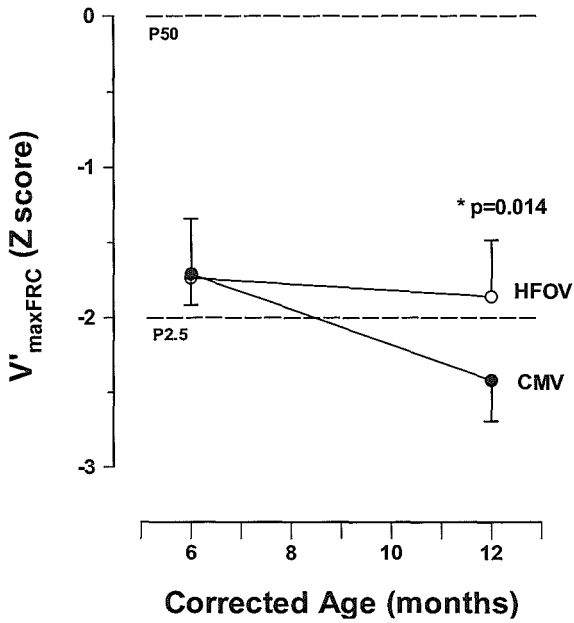

Figure 2. Effect of first intention HFO ventilation on forced expiratory flow. Mean forced expiratory flow at FRC ($V'max_{FRC}$) in Z score (11) in the subgroup of 23 infants who completed both lung function measurements at 6 and 12 months. Individual mean $V'max_{FRC}$ values were inter- or extrapolated to values at exactly 6 and 12 months corrected age. Infants treated

Discussion

In a follow-up study we evaluated lung function in a cohort of 36 very low birth weight infants with CLD, during the first year of life. Furthermore, we studied the relationship between lung function and perinatal patient characteristics. During the first year of life mean forced expiratory flows were below reference values and showed a significant worsening between 6 and 12 months corrected age. At 12 months mean forced expiratory flow was significantly better in the initial HFOV treated group, as compared to the group treated with CMV.
To our knowledge, this is the first study on growth of airway function during the first year of life in VLBW infants with CLD, which also addresses a possible relationship with HFOV. Tepper et al (6) and Iles et al (9) also found decreased forced expiratory flows during the first year of life. However, due to the

survival of younger and smaller infants and differences in treatment modalities, our study population cannot be compared to the population studied by Tepper et al (6). Iles et al (9) studied a population more comparable to our population, but no information about treatment modalities was provided. The decreasing expiratory flows may reflect abnormal functional or anatomical development of the airways (6), which is consistent with pathological findings (13). This could explain the abnormal pulmonary function tests in preterm born children with CLD at school age (3, 4). Alternatively, worsening of airway patency may be due to airway damage and dysfunction of peripheral airways (14), and central airway damage and collapse during dynamic compression (15). Factors such as thickened airway walls, increased smooth muscle layer, disturbed development of airway size and/or airway compliance (16) or altered alveolar architecture may also play a role here (17). Furthermore, the relative decline of $V'max_{FRC}$ during the first year of life was irrespective of the reference equation used (11, 12). The FRC_p was within the normal range at 6 months, and demonstrated a trend to normalization at 12 months of age. This is consistent with previous reports (6-8, 18). With no apparent decline of the mean FRC_p between 6 and 12 months, the change in FRC_p cannot explain the reduction in $V'max_{FRC}$ (19).

First intention HFOV is associated with a shorter time of ventilator-dependency and oxygen-dependency in VLBW infants with RDS (20). Furthermore, it is speculated that early HFOV used with a lung recruitment strategy in combination with surfactant therapy ameliorates acute neonatal lung injury that predisposes some preterm infants to develop CLD (5). The HiFi study group (21) found that the use of HFOV, in comparison with CMV, did not improve $V'max_{FRC}$ at 9 months corrected age. In our study the $V'max_{FRC}$ at 12 months was significantly better in the group initially treated with HFOV, compared to the group initially managed with CMV. This discrepancy could be explained by the difference in timing of measurement or by the fact that in our study HFOV was used as initial therapy. Our data suggest that, in VLBW infants, initial treatment with HFOV is associated with a more favorable development of forced expiratory flow at 12 months corrected age. This finding provides further suggestive evidence that initial HFOV combined with surfactant therapy reduces acute neonatal lung injury (5). Initial ventilation treatment was not intentionally randomized in our study, and therefore this association can not be considered causal. Nevertheless, the HFOV and CMV groups were not different by any perinatal patient characteristic, except for a small difference in birth weight in grams, but not in Z score, and number of surfactant doses. The difference

in birth weight does not explain our finding, as the lower birth weight of the HFOV group would unfavorably affect lung function, whereas we found better results after HFOV. Fewer doses of surfactant were given to the infants who were initially ventilated with HFOV, as compared to CMV. This may reflect reduced respiratory distress following HFOV. We regard the number of surfactant doses not as a confounder, but as a possible first positive outcome of HFOV.

In summary, VLBW infants with CLD, born in the era of surfactant therapy and HFOV, show a worsening of decreased forced expiratory flow during the first year of life. Initial treatment with HFOV was associated with a more favorable development of forced expiratory flow at 12 months corrected age. This finding supports the hypothesis that initial treatment with HFOV in premature neonates prone to develop CLD leads to less airway damage and better medium-term outcome.

Acknowledgement
This study was supported by an unrestricted grant from GlaxoSmithKline, the Netherlands.

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WORSENING OF FORCED EXPIRATORY FLOWS IN INFANTS WITH CLD IN THE FIRST YEAR OF LIFE: A MORE FAVORABLE OUTCOME AFTER HFO VENTILATION

Ward Hofhuis, Johan C. de Jongste, Peter J.F.M. Merkus

When we submitted this manuscript, the sex-specific reference equations for maximal forced expiratory flow at functional residual capacity ($V'max_{FRC}$) based on length by Hoo and coworkers (1) were not published yet. We reanalysed the data in presented in chapter 5 according to these reference equations. In these very low birth weight (VLBW) preterm infants with chronic lung disease (CLD), the mean (SEM) $V'max_{FRC}$ in Z score was -1.8 (0.2) and -1.8 (0.2) at 6 and 12 months corrected age, respectively (Figure 1). These values were significantly below zero (normal value) ($p<0.001$). Between the two measurements there was a mean (95% CI) change of $V'max_{FRC}$ in Z score of 0.0 (-0.3 to 0.3) ($p=0.99$).

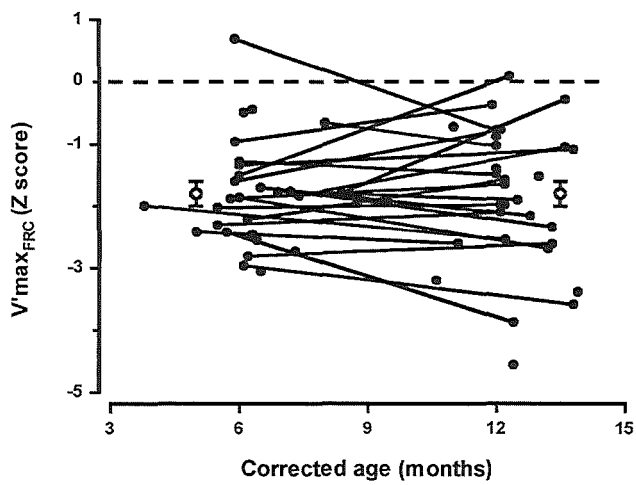

Figure 1. Lung function data of 36 infants with CLD. Individual and mean (SEM) forced expiratory flow at FRC ($V'max_{FRC}$) are expressed in Z score according to Hoo et al (1). Twenty-three infants completed both measurements (connected datapoints).

Infants were subgrouped by initial ventilation strategy: initial high-frequency oscillation ventilation (HFOV) or initial conventional mechanical ventilation (CMV). The HFOV group showed a significant increase in $V'max_{FRC}$ during the first year of life (Mean (SEM) $V'max_{FRC}$ in Z score was -1.6 (0.2) and -1.1 (0.2) at the first and second measurement, respectively (mean (95% CI) difference: 0.5 (0.1 to 0.9), p=0.03), whereas the CMV group showed a significant decrease in $V'max_{FRC}$ during the first year of life (Mean (SEM) $V'max_{FRC}$ in Z score was −2.1 (0.2) and −2.5 (0.2) at the first and second measurement, respectively (mean (95% CI) difference: 0.4 (0.0 to 0.8), p=0.05). At 6 months the mean $V'max_{FRC}$ (Z score) in the HFOV group was not significantly different from the CMV group (Mean (95% CI) difference: 0.5 (-0.8 to 1.1), p=0.10). In contrast, at 12 months the mean (SEM) $V'max_{FRC}$ in Z score was better in the group who received initial HFOV (n=15) as compared to the group who initially received CMV (n=16): -1.1 (0.2) and -2.5 (0.2), respectively (mean (95% CI) difference: 1.4 (0.8 to 2.0), p<0.001) (Table 1). After allowing for the potential confounders (days on ventilation, gestational age and birth weight) using multiple regression analyses, this difference remained significant (p=0.003). However, when both ventilation groups were compared with additional adjustment for number of surfactant dosages, the difference in mean $V'max_{FRC}$ (Z score) at 12 months approached significance (p=0.068).

	HFOV	CMV	Mean difference (95% CI) between HFOV and CMV
$V'max_{FRC}$ at 6 months	-1.6 (0.2)	−2.1 (0.2)	0.5 (-0.8 to 1.1)
$V'max_{FRC}$ at 12 months	-1.1 (0.2)	−2.5 (0.2)	1.4 (0.8 to 2.0)*
Mean difference (95% CI) between 6 and 12 months	0.5 (0.1 to 0.9) #	0.4 (0.0 to 0.8)	

Table 1. HFOV: high-frequency oscillation ventilation. CMV: Conventional mechanical ventilation. $V'max_{FRC}$: Maximal forced expiratory flow at functional residual capacity, expressed in Z score according to Hoo and coworkers (1). *: p<0.001. #: p=0.03. ¶: p=0.05.

Similar results were seen within the subgroup of 23 infants who completed both measurements: the mean (SEM) $V'max_{FRC}$ in Z score was -1.8 (0.2) and −1.7 (0.2) at the first and second measurement, respectively. To study the diffe-

rence between 6 and 12 months precisely, individual mean $V'max_{FRC}$ values were inter- or extrapolated linearly to values at exactly 6 and 12 months corrected age. At 6 and 12 months the mean (SEM) of these adjusted $V'max_{FRC}$ (Z score) values were: -1.8 (0.2) and –1.8 (0.2), respectively (mean (95% CI) change: -0.1 (-0.4 to 0.3). At 12 months the mean (SEM) of the adjusted $V'max_{FRC}$ in Z score was better in the group who received initial HFOV (n=12) as compared to the group who received CMV (n=11): -1.3 (0.2) and -2.3 (0.3), respectively (mean (95% CI) difference: 1.0 (0.2 to 1.7), p=0.012) (Figure 2).

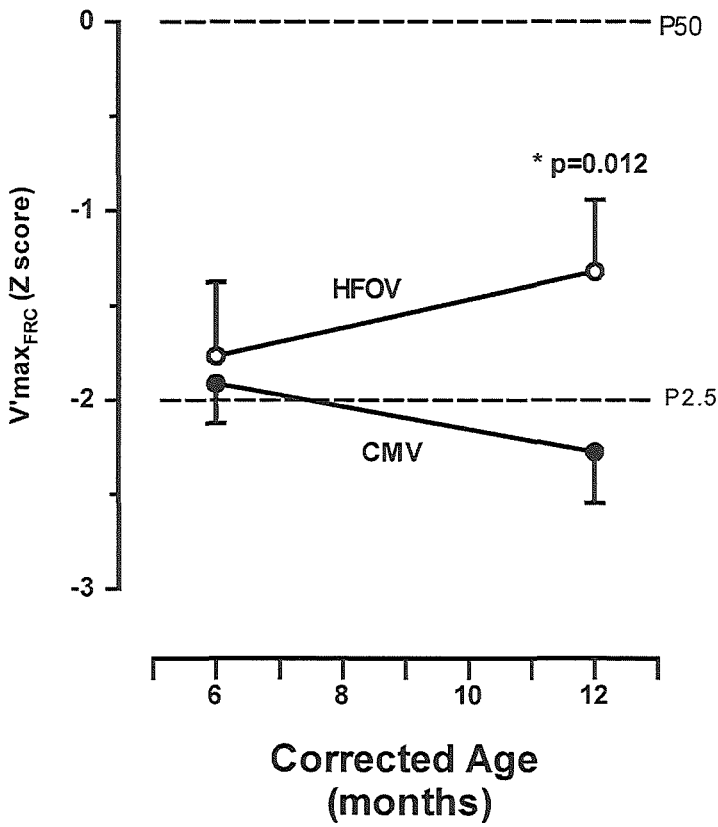

Figure 2. Effect of first intention HFO ventilation on forced expiratory flow. Mean forced expiratory flow at FRC ($V'max_{FRC}$) in Z score (2) in the subgroup of 23 infants who completed both lung function measurements at 6 and 12 months. Individual mean $V'max_{FRC}$ values were inter- or extrapolated to values at exactly 6 and 12 months corrected age. Infants treated with first intention high-frequency oscillation ventilation (HFOV) (open symbols, n=12) are compared to infants treated with conventional mechanical ventilation (CMV) (closed symbols, n=11). Error bars represent SEM.

The question rises which reference equation is the most accurate. We believe that the reference equations by Hoo and coworkers (1) are preferable, as their data consists of the largest number of healthy infants studied so far (n=459), including healthy preterm infants, and the data includes data from four published studies, including that from Tepper and Reister (3-6). Moreover, the reference equations by Hoo and coworkers (1) are sex-specific, and use length as the independent variable. The latter is especially important as infants with BPD tend to be small for age (7, 8). Expressing their lung function data in respect to age will result in Z scores that are too low.

23 paired measurements	6 months	12 months	Mean difference (95% CI)
$V'max_{FRC}$ (ml/s)	68.1 (9.0)	122.7 (11.1)	54.7 (30.4 to 78.9)*
$V'max_{FRC}$ (Z score), according to Tepper and Reister (3)	-1.6 (0.1)	-2..0 (0.1)	-0.4 (-0.6 to -0.1)#
$V'max_{FRC}$ (Z score), according to Sly et al. (9)	-1.7 (0.1)	-2.1 (0.1)	-0.5 (-0.7 to –0.2)¶
$V'max_{FRC}$ (Z score), according to Hoo et al. (1)	-1.8 (0.2)	-1.7 (0.2)	0.1 (-0.3 to 0.4)

Table 2. Mean (± SEM) $V'max_{FRC}$ data expressed in absolute numbers, and in Z scores using different reference equations. *: p<0.001. #: p=0.02. ¶: p=0.004. Note that data may appear different from published data (8) as only paired measurements are shown here.

After this re-analyses, using the new reference equations (1) which are probably superior to the previously available equations, we now show that, in contrast to our published findings (9), forced expiratory flow does not change significantly between 6 and 12 months corrected age in infants with BPD. In table 2, we present the data of the 23 paired measurements, expressed in Z scores using different reference equations. Although there is a significant decrease in expiratory flow during the first year of life using the reference equation by Tepper and Reister (4), and by Sly and coworkers (2), this decrease is not seen using the most recent reference equation by Hoo and coworkers (1). This means that the decline in lung function that was observed in infants with BPD by Süssmuth and coworkers (10), and in healthy preterm infants without BPD observed by Hoo and coworkers (11) cannot be confirmed by our data. This may

be due to the short period of follow-up of 6 months in our cohort, as compared with the 12 months follow-up in these 2 studies (10, 11). From these data it can be concluded that the choice of reference equation significantly influences the results, and that the effect of ventilation strategy on development of airway function may be even more pronounced than previously thought.

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PREDICTIVE VALUE OF INFANT LUNG FUNCTION TESTING FOR AIRWAY MALACIA

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Submitted

Abstract

Airway malacia is present in a small proportion of wheezy infants. The usefulness of Infant Lung Function Testing (ILFT) in ruling out malacia in wheezy infants is unknown. We assessed the negative predictive value of ILFT parameters for airway malacia confirmed by flexible bronchoscopy. Thirty-two term infants (mean (SD) age 11.0 (4.6) months) with chronic wheeze unresponsive to asthma treatment, in which airway malacia was considered, underwent ILFT prior to bronchoscopy. Functional Residual Capacity (FRC_p), maximal flow at FRC ($V'max_{FRC}$) and tidal breathing parameters were obtained. Expiratory flow-volume curves were visually examined for tidal flow limitation. Malacia was observed during bronchoscopy in 20 infants. $V'max_{FRC}$ (Z score) was significantly lower in the group with malacia as compared with the group without. Lung function measurements had a low negative predictive value and sensitivity. While flow limitation during tidal breathing was highly predictive of airway malacia, only half of the infants with malacia had tidal flow limitation. We conclude that in this selected group of infants, lung function testing in infants did not rule out airway malacia in infants with airway obstruction and can therefore not be used to determine which infant should undergo bronchoscopy. However, tidal flow limitation was 100% predictive for airway malacia.

Introduction

Chronic wheeze can be caused by large airway abnormalities including malacia, stenosis or compression of larger airways. Infants with severe tracheobronchomalacia or compression of the larger airways are characterised by stridor, dyspnea, life-threatening apnoeic spells and recurrent pneumonia (1). Treatment of these infants includes aortopexy or long-term CPAP (2, 3). However, infants with mild or moderate symptoms may go unrecognised. They present themselves with chronic or persistent wheeze and often constitute a therapeutic dilemma for the pediatrician (1, 4). When treatment with inhaled corticosteroids and/or β2-agonists fails and symptoms persist, a bronchoscopy may be considered as the next diagnostic step (5). Bronchoscopy may then reveal airway narrowing due to malacia or compression. However, bronchoscopy is an invasive procedure that needs general anaesthesia. Evaluation of flow-volume loops at tidal breathing has found to be helpful in establishing the site of airway obstruction in young children with chronic stridor and/or wheezing (6). Possibly, Infant Lung Function Testing (ILFT) may help in identifying large airway abnormalities. However, there are no studies aimed to determine the clinical value of testing lung function in the management of the infant with a respiratory problem (7). Consequently, the predictive value of ILFT in excluding or recognising airway abnormalities in wheezy infants is unknown.
We therefore assessed the predictive value of ILFT parameters for excluding or recognising large airway abnormalities, diagnosed by bronchoscopy in a group of infants with chronic wheeze, unresponsive to treatment.

Methods and Materials

Study population

We retrospectively evaluated data of all infants who were referred to our tertiary care centre because of suspected airway malacia, between September 1998 and December 2002. Airway malacia was suspected in case of: 1) noisy breathing of a stridorous nature heard centrally, usually both during inspiration and expiration, and/or 2) chronic wheeze unresponsive to ß2-agonists and/or inhaled steroid treatment for at least two months, based on parental report and clinical judgement, with at least two respiratory infections (8). Exclusion criteria were preterm birth, mechanical ventilation, congenital anomalies, meconium aspiration or cystic fibrosis. All infants with a suspected diagnosis of malacia underwent ILFT prior to bronchoscopy and infants were included for analyses

when both ILFT and bronchoscopy were performed. Both ILFT and bronchoscopy were carried out as part of the routine diagnostic procedures for which parents gave permission. Therefore, written informed consent was not obtained and no protocol was submitted to our institutional review board.

Lung function testing

Infants were studied when clinically stable. To prevent the infants from waking up during the measurement they were sedated with chloral hydrate (50-75mg/kg). Heart rate and transcutaneous oxygen saturation (SaO_2) were monitored continuously (Nellcor N2000, Hayward, CA, USA). Functional residual capacity (FRC_p) was measured by means of a modified whole body plethysmograph (Jaeger, Würzburg , Germany). Equipment and procedures were in accordance with guidelines, in which the FRC_p measurement is described in detail (9). Mean FRC_p of 3 to 5 technically acceptable measurements was expressed as Z score using reference data by Stocks et al (9). Maximal flow at FRC ($V'max_{FRC}$), used as a measure of airway patency, was assessed using the end-tidal rapid thoracic compression technique (RTC) using custom-made equipment (Department for Experimental Medical Instrumentation, Erasmus MC - University Medical Centre, Rotterdam, the Netherlands). Equipment and procedures were in accordance with guidelines, in which the RTC- technique is described in detail (10). In short , an inflatable jacket was wrapped around the infant's chest and abdomen with the arms outside the jacket. At end-tidal inspiration the jacket was inflated rapidly, resulting in a forced partial expiratory flow-volume curve. Mean $V'max_{FRC}$ of 3 to 5 technically acceptable measurements was expressed as Z score, also known as standard deviation score, using recently published reference data by Hoo et al. (11). Actual transmission pressure was checked regularly and was around 35% of the jacket pressure. The tidal breathing parameters studied were: Tidal Volume (TV), Breathing Frequency (BF), and Minute Ventilation per kilogram body weight (MV/kg). Flow volume curves were inspected for tidal flow limitation during tidal breathing. Tidal flow limitation was defined as no difference between tidal and forced flow during the last 50% of the forced expired volume, assessed by visual inspection (Fig.1).

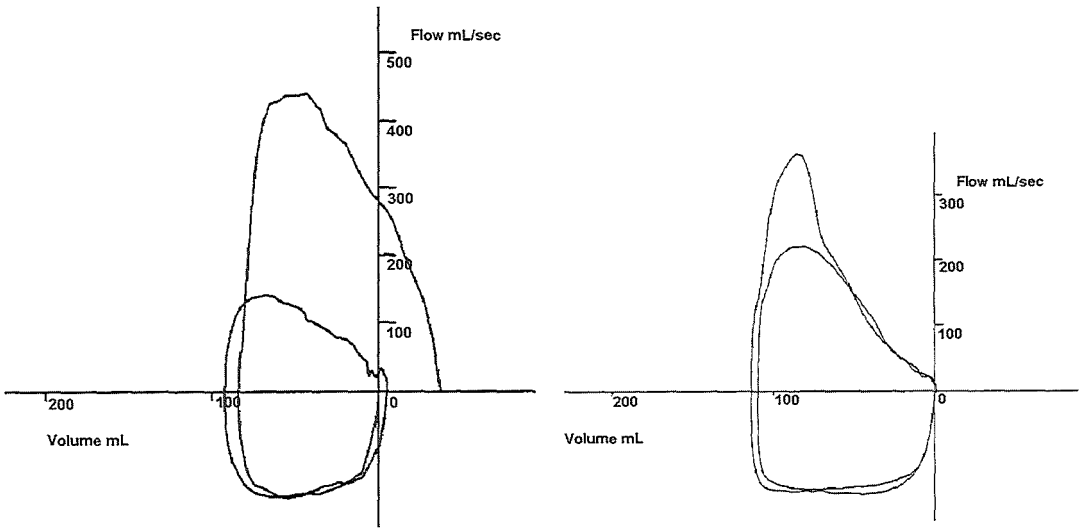

Figure 1. Examples of partial expiratory flow volume curves. Left panel shows a normal curve, where forced flows are well above tidal flows. Right panel shows tidal expiratory flow limitation, indicating significant airways obstruction.

Bronchoscopy

Bronchoscopy was performed under general anaesthesia without muscle paralysis by an experienced paediatric pulmonologist using a flexible bronchoscope (Olympus, type BF3 Tokyo, Japan). Infants were not intubated and breathed spontaneously. We defined an airway malacia as a general or localised weakness of the airway wall that results in excessive >50% narrowing of the lumen during tidal expiration, or whenever intrathoracic pressure increases (for example coughing), in the absence of positive end expiratory pressure. In addition, the airway had to have a cartilage to muscle ratio of approximately 2 or lower (8), because such anatomy may effect compliance to a degree that is clinically relevant (12). Each bronchoscopy was recorded on videotape and independently reviewed by 2 paediatric pulmonologists who were unaware of the ILFT results, patient names, histories, symptoms and suspected diagnosis.

Data analysis

Most infants with a suspected airway malacia will undergo diagnostic bronchoscopy. It is clinically relevant to identify infants who do not have airway malacia, as these infants will not need further diagnostic bronchoscopy. Therefore we chose as primary outcome measure the negative predictive value of ILFT, in excluding airway malacia in wheezy infants. The negative predictive value (NPV) is the number of true negative infants, divided by all infants with a negative test result. Positive predictive value, sensitivity and specificity were also obtained. The positive predictive value (PPV) is the number of true positive infants, divided by all infants with a positive test result. The sensitivity was calculated by the number of true positive infants, divided by the sum of the number of true positive and false negative infants. Specificity was calculated by the number of true negative infants, divided by the sum of the number of true negative infants and false positive infants. Patients were divided into those with and those without airway malacia as diagnosed by bronchoscopy. Anthropometrics and lung function data between groups were compared by independent-samples t tests. The significance level was set at $p < 0.05$.

Results

In the study period a possible diagnosis of malacia was suspected in 32 infants (21 boys). All infants underwent ILFT followed by bronchoscopy, in that order. Both pulmonologists independently identified the same 20 infants (14 boys) with an airway malacia, of whom 12 had tracheomalacia, 4 bronchomalacia and 4 tracheobronchomalacia. Twelve infants had no airway malacia. Anthropometric and ILFT data of these two groups are shown in table 1. There were no significant differences between the two groups with respect to age, length, weight, Tidal Volume, Breathing Frequency and Minute Ventilation. FRC_p was within the normal range and not different between groups. There were no differences related to gender. Mean $V'max_{FRC}$ (Z score) was significantly below normal (Z score =0) for both groups ($p \leq 0.01$) and was significantly lower in the group with airway malacia as compared with the group without airway malacia (mean difference: 1.3 (95% CI: 0.5 to 2.2), p=0.002). Mean $V'max_{FRC}$ (Z score) was significantly lower in the group with airway malacia and tidal flow limitation, as compared with the group without airway malacia (mean difference: 2.0 (95% CI: 1.1 to 3.0), $p<0.001$). However, mean $V'max_{FRC}$ was not significantly lower in the group with airway malacia without tidal flow limitation, as compared with the group without airway malacia (Fig.2).

	Airway malacia n=20	No airway malacia n=12	Mean difference (95% CI)
Age (months)	11.4 (5.1)	10.4 (3.5)	1.0 (ns)
Weight (kg)	8.8 (1.9)	8.7 (1.3)	0.1 (ns)
Length (cm)	73.3 (5.8)	72.8 (5.4)	0.5 (ns)
Tidal Volume (ml)	82.7 (19.6)	86.5 (12.6)	3.8 (ns)
Breathing Frequencies (min^{-1})	32 (9)	31 (4)	1 (ns)
Minute Ventilation ($ml \cdot kg\text{-}1 \cdot min^{-1}$)	300.8 (65.9)	305.9 (35.0)	5.1 (ns)
FRC_p ($ml \cdot kg^{-1}$)	27.4 (5.2)	25.2 (6.6)	2.2 (ns)
FRC_p (Z score)	0.1 (1.3)	-0.6 (1.8)	0.6 (ns)
$V'max_{FRC}$ ($ml \cdot s^{-1}$)	76.6 (44.9)	170.8 (102.8)	94.2 (40.6 to 147.7)†
$V'max_{FRC}$ (Z score)	-2.5 (1.0)	-1.2 (1.3)	1.4 (0.5 to 2.2)$^{\#}$

Table 1. Anthropometric data and results of lung function measurements in infants with and without airway malacia. Values are expressed as mean (SD). FRC_p: functional residual capacity. $V'max_{FRC}$: forced expiratory flow at FRC. ns: not significant. †: p=0.001. $^{\#}$: p=0.002.

Different cut-off points for $V'max_{FRC}$ (Z score) were tested (Table 2). Only when $V'max_{FRC}$ of < -0.5 SD was used as a cut-off for a positive test result, the negative predictive value was 100%, the positive predictive value was 74%, the sensitivity was 100% and the specificity was 36%. However, 7 infants without airway malacia also had a $V'max_{FRC}$ < -0.5 SD.

Within the group of infants with an airway malacia (n=20), 11 infants had tidal flow limitation, whereas tidal flow limitation was not observed in those without airway abnormalities (Figure 2). When the presence of tidal flow limitation was used as a positive test result, the negative predictive value was 57%, whereas the positive predictive value and the specificity were 100% (table 2).

Positive test result	Negative predictive value (%)	Positive predictive value (%)	Sensitivity (%)	Specificity (%)
$V'max_{FRC}$ < -2 SD	62	79	75	67
$V'max_{FRC}$ < -1 SD	75	75	90	50
$V'max_{FRC}$ < -0.5 SD	100	74	100	42
Tidal flow limitation	57	100	55	100

Table 2. The predictive value of ILFT parameters for airway malacia using different definitions of a positive test result.

Discussion

We investigated 32 term infants with chronic wheeze and studied the negative predictive value of ILFT for the exclusion of airway malacia as diagnosed by flexible bronchoscopy. In this selected group of wheezy infants, lung function measurements had a low negative predictive value and sensitivity and, thus, were not useful in ruling out the presence of airway malacia. Flow limitation during tidal breathing was highly predictive (specificity 100%) of airway malacia. However, only half of the infants with airway malacia had tidal flow limitation.
Lung function testing was not capable of discriminating between wheezy infants with and without airway malacia. It remains important to detect those children with airway malacia because of the therapeutic consequences. More important, long-term anti-asthma treatment can be avoided as ß2-agonists do not improve airway patency in infants with malacia (13). In all infants with airway malacia, liberal antibiotic treatment was advised. Nonetheless, the lung function characteristics of infants in this study appeared helpful in ruling in airway malacia. In the case of tidal flow limitation, one might decide not to perform a bronchoscopy, as it is likely that an airway malacia will be found. Radiographic imaging of the mediastinum could then be considered as the next diagnostic investigation to study the relationship between the central airways and large vessels and other structures. However, in most cases ILFT seems to have limited additional diagnostic value and a paediatrician might prefer going right to bronchoscopy which will give a more definitive diagnosis and the opportunity of broncheoalveolar lavage.

It is assumed that $V'max_{FRC}$ is a measure of peripheral airway function, relatively independent of upper airway resistance (14). Since all infants with tidal flow limitation had airway malacia, the present study shows that $V'max_{FRC}$ might also reflect central airflow limitation in infants with airway malacia. The same phenomenon was seen by Tepper and co-workers (15). They studied three infants with three different lesions of the central airways (vascular ring, congenital tracheal stenosis, subglottic polyp). Preoperatively, all three demonstrated severe flow limitation with a relatively constant forced expiratory flow over the tidal volume range. Postoperatively the expiratory flow-volume curves changed to a normal convex shape and $V'max_{FRC}$ returned to normal (15). On the other hand, the central airway narrowing must be very severe to produce tidal flow limitation in the infants with airway malacia. An alternative explanation for our findings can be that the infants diagnosed with airway malacia had a high airway resistance in the small airways with consequently large down stream pres-

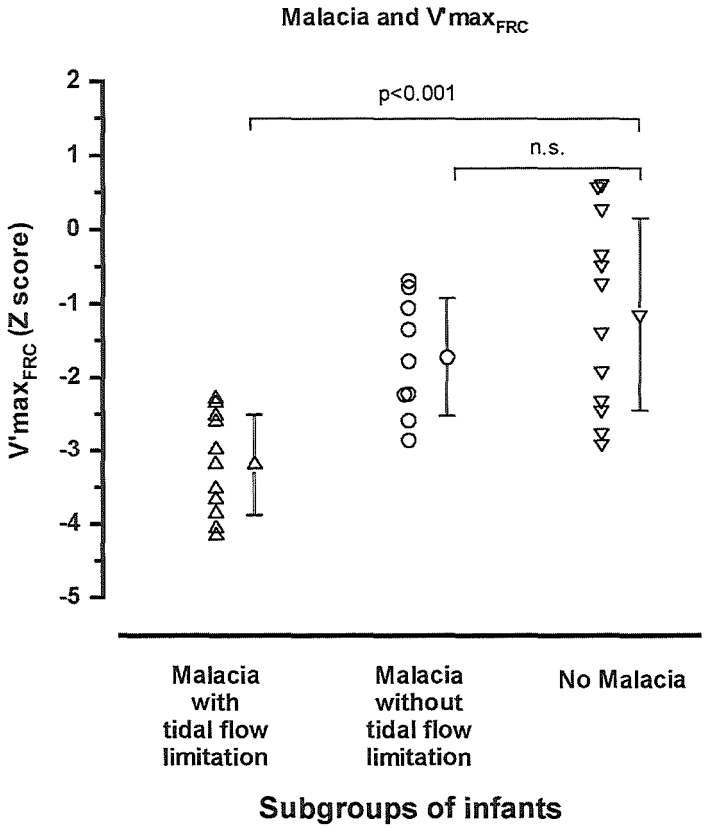

Figure 2. Maximal flow at FRC (V'max$_{FRC}$) in Z score, in subgroups of infants. Within the group of infants with airway malacia, some infants had tidal flow limitation (upward triangles), whereas others had no tidal flow limitation (open circles). Mean V'max$_{FRC}$ (Z score) was significantly lower within the group with airway malacia and tidal flow limitation, as compared to the group without airway malacia (downward triangles).

sure loses. The observed central airway wall mobility could then be explained by increased transmural pressure changes in the trachea, possibly in combination with increased central airway wall mobility. So it remains possible that besides clinically relevant malacia of the trachea or main bronchi, additional peripheral airways obstruction existed in our infants.

In the present study, 55% of the infants with airway malacia had tidal flow limitation. In contrast, Young and co-workers observed tidal flow limitation at 1

month of age in approximately 10% of the infants in a healthy symptom-free term cohort (16). At 6 and 12 months of age these infants no longer had tidal flow limitation, nonetheless they had a significantly reduced lung function as compared to matched controls (16). From the same cohort, Turner and co-workers analysed the data from 3 to 11 years of age (17). The group with tidal flow limitation at 1 month, had increased wheeze at the age of 4 years, and at 6 and 11 years they had increased airway responsiveness and reduced lung function, as compared with other cohort members. Since atopy was not increased in the group who had had tidal flow limitation, Turner and co-workers suggested that flow limitation in early infancy may identify an at-risk group, different from asthma, who has reduced lung function and increased airway responsiveness in later life (17). Whether these respiratory illnesses are based on central airway abnormalities remains to be elucidated, as bronchoscopic investigations were not carried out in the patients of this Australian cohort. However, our study suggests that tidal flow limitation in infancy is associated with airway malacia. Diagnosing an airway malacia remains a difficult and partly subjective issue. Unfortunately, there are still no generally accepted criteria for interpreting bronchoscopic findings (18). A sophisticated way to define airway malacia might be to use a computer aided method to quantify the degree of airway collapse by measuring the airway surface and circumference (19), or a calibrated telescope (20). However, these methods also suffer from lack of precision and still require subjective interpretation. Therefore, we feel that our blinded and unbiased approach in which a diagnosis was made by two experienced clinicians seems as valid. In addition, assessing flow limitation during tidal breathing by visual inspection of the curve is also subjective. We believe that the influence of subjectivity in assessing for flow limitation on the curve is minimal, as the presence of tidal flow limitation is an 'all or nothing' condition. A small difference between tidal and forced expiratory flow means no tidal flow limitation.

We conclude that in this selected group of infants, lung function testing was not capable of ruling out airway malacia in infants with airway obstruction and can therefore not be used to determine which infant should undergo bronchoscopy. The presence of tidal flow limitation however, was 100% predictive for airway malacia, whereas from the absence of tidal flow limitation no conclusions could be drawn.

Acknowledgement
This article is supported with an unrestricted grant from GlaxoSmithKline, the Netherlands

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LUNG FUNCTION DURING THE FIRST YEAR OF LIFE IN INFANTS FOLLOWING EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

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Submitted

Abstract

Term neonates with reversible cardio-respiratory failure may be treated with veno-arterial extracorporeal membrane oxygenation (ECMO). We evaluated lung function longitudinally at 6 and/or 12 months of age in a group of ECMO survivors. Functional residual capacity (FRC_p) and forced expiratory flow at FRC ($V'max_{FRC}$) were measured and expressed as Z score. We studied 38 infants (19 males). Mean (SD) birth weight and gestational age were 3456 (493) grams and 40.2 (1.4) weeks, respectively. Twenty-one infants received ECMO for meconium aspiration syndrome (MAS), 8 for congenital diaphragmatic hernia (CDH), 3 for sepsis, 3 for persistent pulmonary hypertension of the neonate (PPHN) and 3 for respiratory distress syndrome of infancy (IRDS). Twenty-eight infants were evaluated at 6 months and 26 infants at 12 months; 16 infants completed both measurements. Mean (SEM) FRC_p in Z score was 0.0 (0.2) and 0.2 (0.3) at 6 and 12 months respectively. Mean (SEM) $V'max_{FRC}$ in Z score was significantly below normal value (Z score=0) ($p<0.001$) at 6 and 12 months: -1.4 (0.2) and −1.1 (0.2), respectively (Mean (95% CI) difference: 0.3 (-0.1 to 0.7)). When subgrouped by diagnosis, there were no significant differences in lung function between groups. However, at 12 months of age, infants with CDH had a higher mean FRC_p in ml/kg as compared to infants with MAS. We conclude that during the first year of life, these infants who received ECMO support have normal lung volume and normal development of expiratory flow at a level below average. These data suggest that in infants with respiratory failure, ECMO treatment contributes to normal lung function development.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a supportive intensive-care technique mainly used for term newborns with acute reversible cardio-respiratory failure and a high mortality risk with conventional management. Conventional management ranges from pressure controlled ventilation to high-frequency oscillatory ventilation (HFOV), with or without inhaled nitric oxide (NO). ECMO consists of prolonged cardiopulmonary bypass while 'resting' the lungs and using minimal ventilator settings. It is thought that this promotes lung healing and prevents further injury from high oxygen concentration, volutrauma and barotrauma (1). The UK ECMO trial conferred a survival advantage of ECMO over conventional management, without a concomitant increase in severe disability (2, 3). However, ECMO may promote survival of infants with severe respiratory dysfunction, who would otherwise have died. This could result in a poor respiratory status in infants treated with ECMO. On the other hand, ECMO avoids prolongation of aggressive ventilation and consequent barotrauma, which has been shown to be associated with subsequent alterations in respiratory mechanics (4, 5) . Hence, investigation of the respiratory function of survivors is essential to assess whether or not ECMO results in a survival advantage (6). Several groups studied respiratory function in infants during or shortly after ECMO (7-9), at 6 months (10) or at 12 months (6). These studies found a reduction in pulmonary function during the first year of life, confirming sequelae of severe respiratory disease despite ECMO. To date, longitudinal data are only available for infants during or shortly after ECMO (7, 8). To our knowledge, no study evaluated lung function in ECMO survivors longitudinally during the first year of life. Therefore, we evaluated lung function in a prospective longitudinal study at 6 and 12 months of age, in a group of ECMO survivors. Furthermore, we studied the relationship between lung function and perinatal patient characteristics.

Methods

Subjects

A follow-up study was conducted in neonates who received veno-arterial ECMO support between February 2001 and May 2003 at the Pediatric Surgical Intensive Care Unit of the Sophia Children's Hospital. ECMO support was given in case of reversible severe respiratory failure and an estimated mortality risk of 80%. Criteria used to define this mortality risk were an oxygenation

index > 40 in 3 to 5 subsequent arterial blood gases, an alveolar arterial oxygen gradient ($AaDO_2$) >600 during 8 hours with a FiO_2 of 100% and signs of barotrauma. Exclusion criteria for ECMO support were: (a) gestational age < 34 weeks or a birth weight of <2 kg, b) intraventricular hemorrhage grade II, c) known bleeding disorders, d) high pressure ventilation for more than 10 days prior to ECMO support, e) any reason to question continuation of conventional management (for example a major congenital or chromosomal anomaly). Artificial ventilation was administered by conventional mechanical ventilation (CMV) (Babylog 8000, Dräger Medical, Germany) or high-frequency oscillatory ventilation (HFOV) (Sensormedics, the Netherlands). The initial ventilation strategy was not randomized in our study. The study was part of a structured follow-up program, including lung function, growth and developmental parameters untill 12 years of age. According to the Dutch law, approval from a medical ethical committee was therefore not required. All parents gave written informed consent.

Lung function

Lung function measurements were performed at 6 and 12 months of age, when the infants had no signs of infection or acute respiratory symptoms. To prevent the infants from waking up during the measurements, they were sedated with choral hydrate (50-75 mg/kg). Airway resistance was measured using the interrupter technique (R_{int}) (MicroRint, Micro Medical Ltd, Rochester, UK). Functional residual capacity (FRC_p) was measured by means of a modified whole body plethysmograph (Jaeger, Würzburg, Germany). Mean FRC_p of 3 to 5 technically acceptable measurements was expressed as Z score (11). Forced expiratory flow at FRC ($V'max_{FRC}$), used as a measure of airway patency, was assessed using the end-tidal rapid thoracoabdominal compression (RTC) technique (Custom-made equipment. Department of Experimental Medical Instrumentation, Erasmus University Medical Center, Rotterdam). Equipment and procedures were in accordance with guidelines (11, 12). Mean $V'max_{FRC}$ of 3 to 5 technically acceptable measurements was expressed as Z score (13).

Analysis

Lung function measurements at 6 and 12 months were compared using mixed-model ANOVA (SAS, PROC MIXED). Where applicable, the difference in lung function was evaluated using paired Student's T-test. The influence of various perinatal variables on level of lung function was evaluated by multiple regression analyses. The significance level was set at $p < 0.05$.

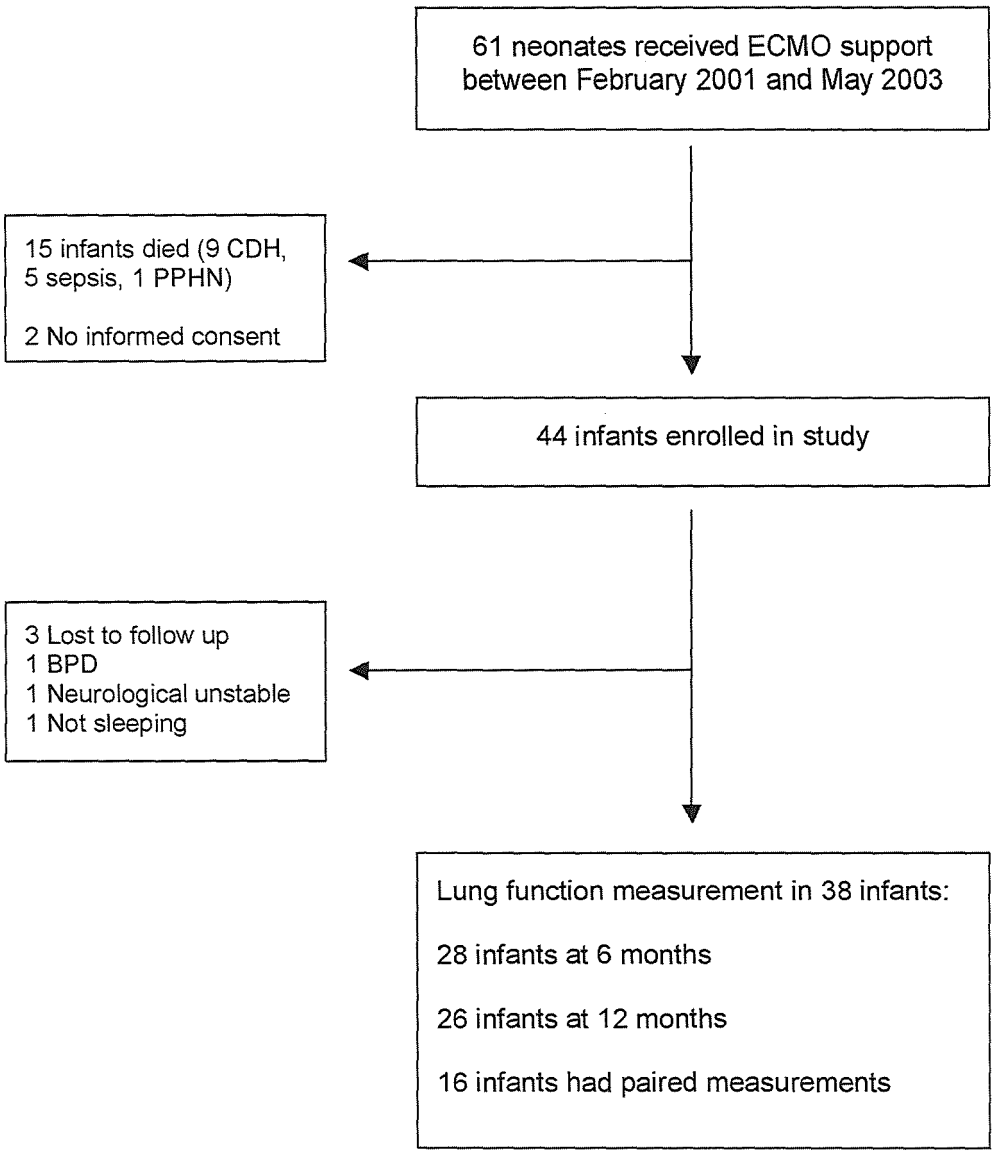

Figure 1. Patient flow through the study.

	Total group n=38	Measurement at 6 months n=28	Measurement at 12 months n=26
Gestational age (wk)	40.2 (1.4)	40.2 (1.3)	40.3 (1.4)
Birth weight (g)	3456 (493)	3393 (497)	3472 (524)
Males	19	14	14
MAS	21	16	14
CDH	8	5	5
Sepsis	3	1	3
PPHN	3	3	3
IRDS	3	3	1
Inborn / Outborn patients	4	3	2
Age at receiving ECMO support (hours)	22 (5 - 252)	21 (5 - 168)	23 (5 - 252)
FiO_2 prior to ECMO	1 (0)	1 (0)	1 (0)
Oxygenation index prior to ECMO*	38 (10 - 167)	40 (10 - 143)	40(10 -167)
NO treated newborns	32	24	22
Inhaled NO prior to ECMO (ppm)	20 (0 - 40)	20 (0 - 40)	20 (0 - 40)
Duration of ECMO support (hours)	123 (53 - 253)	122 (53 - 227)	126 (53 - 253)
Duration of mechanical ventilation (days)#	9 (3 - 116)	10 (3 - 116)	9 (3 - 40)
Duration of oxygen dependence (days)	25 (5 - 146)	28 (9 - 146)	21 (5 - 76)
Surfactant treated newborns	15	11	10
Length of stay at the ICU	18 (6 - 154)	17 (6 - 154)	15 (8 - 67)

Table 1. Demographic characteristics. Data given are number of infants or mean (SD) or median (range). Shown are the total group, and the subgroups of infants measured at 6 months, and measured at 12 months of age. Sixteen infants completed both measurements. GA: gestational age. MAS: Meconium aspiration syndrome. CDH: Congenital diaphragmatic hernia. PPHN: Persistent Pulmonary Hypertension of the Newborn. IRDS: Respiratory distress syndrome of infancy. HFOV: high-frequency oscillatory ventilation. FiO_2: Fraction of inspired oxygen. NO: Nitric oxide (parts per million) *: Oxygenation index was calculated as: [(Mean airway pressure * FiO_2)/PaO_2] * 100. ICU: Intensive care unit. #: Duration of mechanical ventilation includes mechanical ventilation prior and after ECMO treatment.

Results

Between February 2001 and May 2003, 61 infants received ECMO treatment of which 46 infants survived untill discharge (75%). Lung function measurements were performed in 38 infants (Figure 1). Sixteen infants were measured both at 6 and 12 months of age. Reasons for not completing both measurements were

being younger than 12 months at the end of the study (n=10), failure to sleep during the procedure (n=5), recurrent airway infections (n=3), and lost to follow-up (n=4). Demographic characteristics of the cohort of 38 infants are shown in table 1. Reasons for ECMO support were meconium aspiration syndrome (MAS) (n=21), congenital diaphragmatic hernia (CDH) (n=8), persistent pulmonary hypertension of the newborn (PPHN) (n= 3), sepsis (n=3) and respiratory distress syndrome of infancy (IRDS) (n=3). All CDH infants had undergone surgical repair after successfull decanulation from the ECMO-circuit. The first and second lung function measurements were performed at a mean (SD) age of 6.3 (0.5) and 12.2 (0.5) months, respectively. The results of the R_{int}, FRC_p and the $V'max_{FRC}$ measurements are shown in table 2.

	Measurement at 6 months (Mean ± SEM)	Measurement at 12 months (Mean ± SEM)	Mean difference (95% CI)
R_{int} (kPa/l/s)	3.5 (0.2)	3.2 (0.2)	-0.3 (-0.8 to 0.2)
FRC_p (ml/kg)	27.3 (1.0)	28.1 (1.1)	0.7 (-1.3 to 2.8)
FRC_p (Z score)*	0.0 (0.2)	0.2 (0.3)	0.3 (-0.2 to 0.8)
$V'max_{FRC}$ (ml/s)	120.0 (12.2)	200.5 (16.3)	80.5 (49.6 to 111.4)*
$V'max_{FRC}$ (Z score)†	-1.4 (0.2)#	-1.1 (0.2)#	0.3 (-0.1 to 0.7)

Table 2. Results of lung function measurements in infants following ECMO during the first year of life. At measurement 1 and 2, the mean (SD) corrected age was 6.3 (0.5) and 12.2 (0.5) months, respectively. R_{int}: airway resistance measured by means of interrupter technique. FRC_p: functional residual capacity. $V'max_{FRC}$: forced expiratory flow at FRC. *: p<0.001. #: Significantly below normal (Z score = 0) (p<0.001).

For the whole group, mean $V'max_{FRC}$ in Z score was significantly below zero (normal value) both at the first and second measurement (p<0.001) (table 2, figure 2). Between the two measurements there was a mean (95% CI) change of $V'max_{FRC}$ in Z score of 0.3 (-0.1 to 0.7) (p=0.10). Similar results were seen within the subgroup of 16 infants who completed both measurements: Mean (SD) $V'max_{FRC}$ in Z score at 6 and 12 months was -1.3 (0.9) and –1.0 (1.1), respectively, with a mean (95% CI) difference of 0.3 (-0.1 to 0.8)(p=0.16).

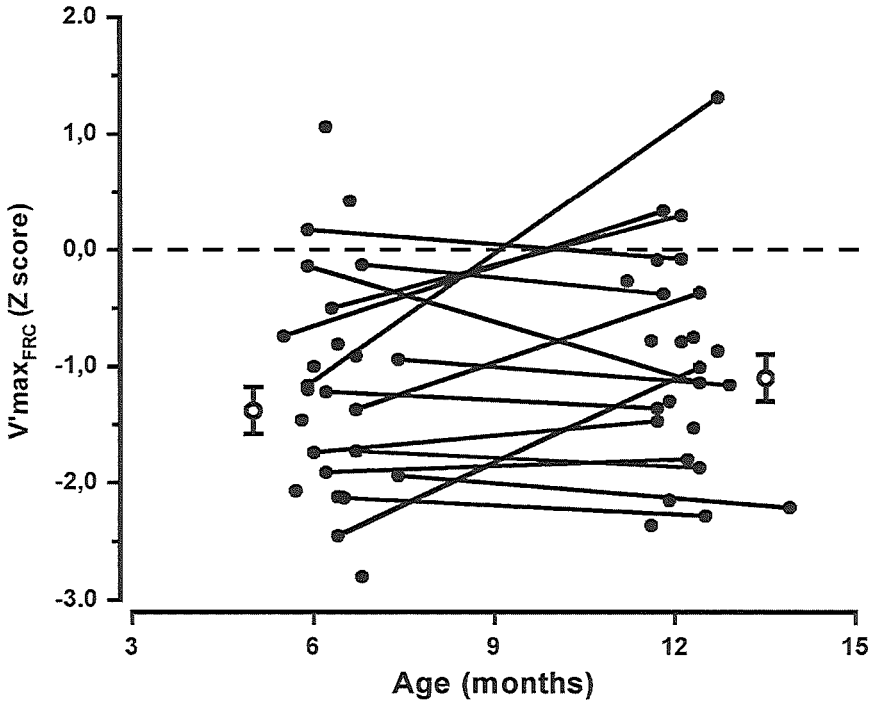

Figure 2. Lung function data of 38 infants following ECMO. The first (n=28) and second (n=26) measurement were done at a mean (SD) age of 6.3 (0.5) and 12.2 (0.5) months, respectively. Mean (SEM) V'max$_{FRC}$ was -1.4 (0.2) and -1.1 (0.2) at the first and second measurement respectively. Sixteen infants completed both measurements (connected datapoints).

Infants who received ECMO for MAS or CDH were analyzed separately. Their lung function results are shown in table 3. At 12 months of age, infants with CDH had a higher mean FRC_p in ml/kg as compared to infants with MAS. In CDH infants there was a trend that FRC_p in Z score was above the reference value (Z score=0) at 12 months of age (Mean (95% CI) difference: 1.3 (-0.1 to 2.6) (p=0.07).

There was a significant correlation between days of mechanical ventilation (prior and after ECMO) and FRC_p in Z score at 6 months (r=0.42, p=0.02) and at 12 months (r=0.59, p=0.003). None of the other perinatal patient characteristics, including age at receiving ECMO or the duration of ECMO, correlated with lung function parameters.

	Measurement at 6 months			Measurement at 12 months		
	MAS n=16	CDH n=5	Mean difference (95% CI)	MAS n=14	CDH n=5	Mean difference (95% CI)
R_{int} (kPa/l/s)	3.9 (0.3)	3.4 (0.6)	-0.5 (-1.9 to 0.8)	3.3 (0.3)	3.0 (0.5)	-0.4 (-1.4 to 0.7)
FRC_p (ml/kg)	27.4 (1.5)	29.1 (2.9)	1.8 (-4.7 to 8.3)	26.5 (1.4)	33.2 (2.5)	6.6 (1.0 to 12.2)*
FRC_p (Z score)	0.0 (0.3)	0.5 (0.6)	0.6 (-0.7 to 1.9)	-0.1 (0.4)	1.3 (0.7)	1.4 (-0.2 to 2.9)
$V'max_{FRC}$ (ml/s)	102.7 (15.8)	106.4 (27.4)	3.6 (-59.4 to 66.6)	199.5 (26.6)	219.6 (44.6)	20.1 (-81.6 to 121.8)
$V'max_{FRC}$ (Z score)	-1.8 (0.2)	-1.2 (0.4)	0.6 (-0.3 to 1.5)	-1.2 (0.3)	-0.6 (0.5)	0.6 (-0.6 to 1.7)

Table 3. Mean (SEM) lung function data between infants who received ECMO because of meconium aspiration syndrome (MAS) or congenital diaphragmatic hernia (CDH). *: p= 0.03.

Discussion

In this study we longitudinally evaluated lung function during the first year of life in a cohort of 38 infants who received ECMO support. Furthermore, we studied the relationship between lung function and perinatal patient characteristics. We found normal lung volume and subnormal forced expiratory flow during the first year of life.

To our knowledge, this is the first longitudinal study on changes of airway function during the first year of life in survivors of ECMO. Two cross-sectional studies were published. Greenspan and colleagues (9) studied the $V'max_{FRC}$ after ECMO in 25 infants of approximately 1 month of age. Using the normative data by Sly and colleagues (12), the $V'max_{FRC}$ in Z score at 1 month of age in this study was approximately -0.3 SD. From their publication it was not feasible to calculate the $V'max_{FRC}$ in Z score using the normative data by Hoo and colleagues, as no information about length at time of measurement was provided. Beardsmore and colleagues (6) found a $V'max_{FRC}$ at 12 months of -1.6 SD in Z score (personal communication A. Hoo), using the normative data by Hoo and colleagues (13). Using the normative data by Sly and colleagues (12), the $V'max_{FRC}$ is approximately -1.7 SD. These cross-sectional data from different studies suggest a decrease in forced expiratory flow during the first year of life in ECMO survivors. This is in contrast with our longitudinal data, which show normal development of $V'max_{FRC}$ at a level below average, with normal FRC_p. It can be speculated that different clinics have ranging criteria for ECMO aswell as their pre-ECMO approach of the patient. For example, in our clinic infants were placed on ECMO

earlier as compared with the infants in the study by Beardsmore and colleagues (6), 22 hours versus 32 hours respectively. This could explain discrepant follow-up results, however, this is difficult to substantiate.

It is not clear what the separate effect of the mechanical ventilation or the underlying disease is on lung function. One could hypothesize that if infants received ECMO support earlier, the duration of mechanical ventilation is reduced which could lead to less lung damage, and as a consequence improved lung function. However, we did not find a correlation between lung function and the age (hours after birth) at receiving ECMO. In contrast, we did find a significant correlation between days of mechanical ventilation (prior and after ECMO) and FRC_p in Z score at 6 and at 12 months. A possible explanation could be that mechanical ventilation leads to peripheral airway damage, which could lead to air trapping. Conversely, one could speculate that the increased lung volume after prolonged ventilation is not the result of this ventilation, but infants with increased lung volume, possibly due to increased gas trapping, were more likely to require prolonged ventilation.

When infants were subgrouped by primary reason for ECMO, infants with CDH had a higher mean FRC_p in ml/kg at 12 months of age, as compared to infants with MAS. When expressed in Z score, there was a trend that FRC_p was above the reference value (Z score=0) at 12 months of age. This last finding did not reach significance, possibly due to lack of power. Helms and Stocks found normal lung volumes (FRC_p) in 4 infants and low lung volumes in 5 infants with a surgically repaired CDH (14). They concluded that a normal lung volume in these infants not necessarily means that intrauterine lung development has been normal. The development of a normal lung volume later in infancy (15) may be due to alveolar distension and destructive emphysema of a hypoplastic lung (16, 17). Nagaya and co-workers studied lung volume, by computed tomography scan, and pulmonary perfusion in infants following surgical repair of CDH and ECMO treatment (18). They found that these infants had low ipsilateral lung volumes (61% of contra-lateral lung volume) at 3 months of age, which increased during follow-up to 88% of contralateral lung volume. In contrast, the perfusion of the affected side remained low, or decreased to below the initial value. It was concluded that the lung of the affected side has little ability to develop arterial branches and that enlargement of lung volume may depend on overexpansion or progressive emphysema, rather than tissue growth (18). To our knowledge, our study is the first that suggests an increased lung volume in infants following surgical repair of CDH and ECMO treatment.

Possibly, with the introduction of ECMO, more severe cases of CDH have survived, with consequently more severely hypoplastic lungs. We speculate that the increase in lung volume is most likely explained by hyperinflation of existing alveoli. We did not find a correlation between age at receiving ECMO and any lung function parameter. This is in contrast with Greenspan and coworkers who found that infants who received ECMO late had lower $V'max_{FRC}$ at discharge, as compared with infants who received ECMO earlier (9). However, as Greenspan and coworkers studied the infants at discharge, at approximately 1 month of age, an effect of age at receiving ECMO on lung function may only be present during the first months of life.

We conclude that during the first year of life, these infants who received ECMO support have normal lung volume and normal development of expiratory flow at a level below average. These data suggest that in infants with respiratory failure, ECMO treatment contributes to normal lung function development.

Acknowledgement
WH and MNH contributed equally to the manuscript.

This study was supported by a unrestricted grant from GlaxoSmithKline, the Netherlands

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Summary

Infant lung function testing has been around for 50 years or more. Still it is not clear to what extent testing of lung function in infants during the first 2 years of life adds materially to clinical management (1). Most studies on lung function testing in infants were performed for research purposes, focussing on physiology, pathophysiology, drug or therapy trials, or lung function methodology. Nonetheless, knowledge gained from clinical trials improve treatment in the long term, and, therefore, has clinical impact (1). A minority of the published studies on lung function testing in infants were performed for clinical purposes, such as follow-up of disease or clinical management. Moreover, there are no studies to determine the clinical added value of testing lung function in the management of the infant with a respiratory problem (1).
Therefore, the primary objective of this thesis was to evaluate lung function in infants with several respiratory disorders and to study the effect of treatment on lung function in infants with recurrent wheeze. Secondary objectives were to study the clinical value of lung function testing in the management of the infant with a respiratory problem, and to study the relationship between lung function and patient characteristics.

Chapter 1 reviews the literature regarding the methodology of infant lung function testing, as well as studies on lung function testing in infants performed for clinical purposes.

Chapter 2 contains a general introduction to the thesis, and discusses the study aims in detail.

In chapter 3, we studied the effect of bronchodilators (β_2-agonists) on the lung function in infants with recurrent wheeze or airway malacia. The study aims were to assess the nature and magnitude of the bronchodilator response, and to determine whether a negative effect of β_2-agonists on forced expiratory flow ($V'max_{FRC}$) is more pronounced in infants with airway malacia, compared to infants with wheeze. We found that only in infants with wheeze, inhaled β_2-agonists gave a significant reduction in mean $V'max_{FRC}$. Infants with malacia were not more likely to worsen after β_2-agonists than infants with recurrent

wheeze. Therefore, we rejected the hypothesis that a negative effect of β_2-agonist administration on $V'max_{FRC}$ is more likely in infants with airway malacia, compared to infants with wheeze. Our study suggests that a possible explanation for this finding could be that baseline $V'max_{FRC}$ was significantly lower in the malacia group, with flows sometimes limited to (near) tidal levels, and thus leaving little room for further deterioration. Conversely, at these levels a small deterioration in lung function may be clinically more significant than a larger deterioration in a child with a better lung function, as was assessed in the wheeze group.

In chapter 4, we assessed the effect of inhaled steroids on lung function in infants with persistent or recurrent wheeze, in a double-blind randomized placebo-controlled study (AIR-study). We hypothesized that treatment with fluticasone propionate 200 mg (FP200) daily for 3 months in these infants improves lung function and symptom scores, as compared with placebo. The second aim was to evaluate whether infants with atopy and/or eczema respond better to FP200 treatment as compared with non-atopic infants. We found that a 3 months treatment with FP200 dialy, inhaled via the babyhaler, did not improve lung function in infants with recurrent or chronic wheeze. Therefore, we rejected the hypothesis that FP improves lung function in infants with recurrent or persistent wheezing. However, after 6 weeks of treatment, the infants treated with FP200 had significantly more symptom free days and a significant reduction in mean daily cough score, as compared with placebo. After 13 weeks of treatment, these findings were not statistically different between the study arms. Separate analysis of treatment effect in infants with atopy or eczema showed no effect modification. A possible explanation for the lack of response in lung function to FP200 in our study could be that the majority of infants with wheezing have transient conditions associated with diminished airway function at birth due to small airways (2). The presence of small airways predispose many infants to wheezing in association with common viral infections (2). The effect of ICS in non-asthmatic viral wheeze is uncertain. Nonetheless, our study confirms other studies (3, 4) that show a reduction in symptoms after FP treatment in infants with recurrent or persistent wheeze. Therefore, we concluded that although FP200 did not improve lung function, it could be considered for reducing symptoms in infants with recurrent or persistent wheeze.

In chapter 5, we evaluated lung function during the first year of life in prematurely born infants of very low birth weight with chronic lung disease

(CLD), in the era of surfactant therapy and high-frequency oscillation ventilation (HFOV). We concluded that in these very low birth weight infants with CLD have decreased forced expiratory flows that worsen during the first year of life. Furthermore, initial treatment with HFOV was associated with a more favorable outcome of forced expiratory flows at 12 months corrected age. We speculated that the decreasing expiratory flows might reflect abnormal functional or anatomical development of the airways. If this is the result of preterm birth or mechanical ventilation, or a combination, remains to be elucidated. However, other studies provide evidence that prematurity per se impairs subsequent lung growth (5, 6). In the addendum to chapter 5 we reanalyzed the data presented in chapter 5 using more recent sex-specific reference equations for $V'max_{FRC}$.
We now show that forced expiratory flow does not change significantly between 6 and 12 months corrected age in infants with CLD. Moreover, infants who received initial HFOV showed a significant increase in forced expiratory flow during the first year of life. From these data it can be concluded that the choice of reference equation significantly influences the results, and that the effect of ventilation strategy on development of airway function may be even more pronounced than previously thought.

In chapter 6, we studied the diagnostic value of Infant Lung Function Testing (ILFT) for airway malacia in wheezy infants. We found that lung function measurements had a low negative predictive value and low sensitivity. Flow limitation during tidal breathing was 100% predictive of an airway malacia. However, only half of the infants with airway malacia had tidal flow limitation. We concluded that lung function testing in infants was not capable of ruling out airway malacia in infants with airway obstruction and can therefore not be used to determine which infant should undergo bronchoscopy. Nonetheless, our study strongly suggests that the presence of flow limitation during tidal breathing is associated with the presence of airway malacia.

In chapter 7, we evaluated longitudinally lung function during the first year of life in survivors of extracorporeal membrane oxygenation (ECMO) support. We found that during the first year of life, these infants who received ECMO support have normal lung volumes and normal expiratory flow that did not worsen upon follow-up. These data suggest limited effects of ECMO on lung function development. In the subgroup of infants who received ECMO for congenital diaphragmatic hernia (CDH), there was a trend that lung volume was above reference value. We speculate that the increase in lung volume is

most likely explained by hyperinflation of existing alveoli resulting in an emphysematous lung.

The studies in this thesis show that research in the field of lung function testing in infants has moved from methodological issues towards clinical applications. This development is mainly the result of publications of guidelines for infant lung function testing and standardization of the equipment used, by the European Respiratory Society en de American Thoracic Society (ERS/ATS) (7-10). As a result, normative data have become available for different lung function methods, allowing comparison of data from different centers. In addition, several biomedical engineering companies have marketed equipment with specifications according to the guidelines given by the ERS/ATS. These developments are a necessity for wide applications of infant lung function testing in a clinical setting, such as collaborative studies and multicenter drug trials in infants with airway disease (11). On the other hand, there are high costs for buying complete recording systems and training the staff. In addition, most methods require sedation of the infant. Therefore, infant lung function measurements will probably be established primarily in larger, mostly academic, centers. The forthcoming challenges for those involved in this field will be to develop methods that are cheap to buy and simple to use, still providing essential information. These methods should be applicable in infants without sedation. When this has been achieved, infant lung function testing may even move out of the clinic (11).

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General discussion and directions for future research

9

General discussion

In the next paragraphs, the most relevant findings of this thesis and the practical implications are discussed. In addition, suggestions for future research are provided.

Infants with recurrent or persistent dyspnea

There is no clear benefit regarding the treatment with beta2-agonists and/or inhaled steroids in the management of recurrent or persistent dyspnea in the first two years of life. Although no evidence based arguments exist for these treatment regimes, they are prescribed on a large scale. Further studies are needed to evaluate these treatment regimes in infancy. Therefore, we aimed to evaluate the effect of bronchodilators (beta2-agonists) on the lung function in infants with recurrent wheeze or airway malacia (Chapter 3). We concluded that mean $V'max_{FRC}$ is reduced and did not improve after inhalation of β_2-agonists in infants with malacia or wheeze. In infants with wheeze, but not in infants with malacia, there was a significant reduction in mean $V'max_{FRC}$ after inhalation of β_2-agonists.

An alternative explanation for our finding that children with malacia were not more likely to worsen after β_2-agonists, could be that in malacia, forced expiration assessed with the RTC-technique is affected by dynamic compression to such an extent that a further reduction of smooth muscle tone by bronchodilation does not result in further deterioration of airway patency.

The significant reduction in mean $V'max_{FRC}$ in the wheeze group supports the recent conclusion of a Cochrane-review that there is no clear benefit of β_2-agonists in the treatment of wheezy infants during the first 2 years of life, although there is conflicting evidence (1). Possible explanations for the lack of efficacy of β_2-agonists on lung function and/or clinical parameters in wheezy infants are discussed below. The discussion is based on Hofhuis and coworkers. β_2-agonists in infants with wheeze, often ineffective. Nederlands Tijdschrift voor Geneeskunde. 2003 (2).

EXPLANATIONS FOR LACK OF EFFICACY OF β_2-AGONISTS ON LUNG FUNCTION:
First, measurement of $V'max_{FRC}$ relies on FRC not changing between forced expirations. There is abundant evidence that FRC is not stable and shifts with dynamic events such as changes in airway caliber (3), sleep state or addition of dead space (4, 5). A lower FRC could have been established after bronchodilation and explain a lower flow at this new FRC. However, a lower flow for this reason could also be clinically important (6). We found a non-significant change in FRC after bronchodilation, making it unlikely that this is the explanation for the lack of efficacy of β_2-agonists on $V'max_{FRC}$ (7).

The lack of efficacy of β_2-agonists on lung function in wheezy infants could also be explained by the fact that symptoms are not based on reversible bronchoconstriction. Only in the minority of wheezy children until the age of 4 years, are the symptoms the result of asthma (8). In the majority of infants (about 60%) with wheezing the symptoms are based on transient conditions associated with diminished airway patency (8). Most infants who wheeze during their first year of life have a pre-existent diminished lung function, as compared with asymptomatic infants (9). It seems plausible that in wheezy infants who respond to β_2-agonists, the dyspnea is the result of reversible bronchoconstriction. However, there is no evidence that those infants have an increased risk for asthma later in life. Possibly, a future study could address this hypothesis by follow-up of infants who wheeze during their first year of life, and comparing those who responded well to β_2-agonists with those who didn't.

Another explanation could be that reduction of smooth muscle tone by bronchodilation could make the airways more compliant, and therefore more collapsible, resulting in increased dynamic compression and reduced forced expiratory flows. This hypothesis can be explained by the fact that the airways of infants are more compliant than the airways of older children (10) since smaller airways have less cartilage (11). Adult airways with little cartilage are known to be dependent on smooth muscle tone for their rigidity (12). A reduction of smooth muscle tone will make these airways more compliant (Figure 1) and will increase their collapsibility (12). Possibly, this applies also to the airways of young children. During a forced expiration the small airways could collapse partially or even completely, resulting in a decreased forced expiratory flow (13, 14). This paradoxical response to β_2-agonists can be of major clinical importance as infants with dyspnea use forced expirations during tidal breathing to maintain sufficient oxygenation (14). This hypothesis that smooth muscle tone is important for maintaining airway patency is supported by the

fact that airway patency can improve after low concentrations of histamine in young wheezy children (15). As children grow older their airways will contain relatively more cartilage which makes the airway less compliant (i.e. stiffer) (11). As a consequence, the small airways will be less dependent on smooth muscle tone for their rigidity and a possible negative effect of β_2-agonists will be less evident. This statement is supported by the finding that there was no positive effect of β_2-agonists in infants younger than 18 months, while infants older than 20 months showed a decrease of airway resistance after β_2-agonists (16). This age-effect can not be explained by the absence of (active) β_2-receptors in infants, as there is abundant prove that infants have active β_2-receptors in their airways (17-19).

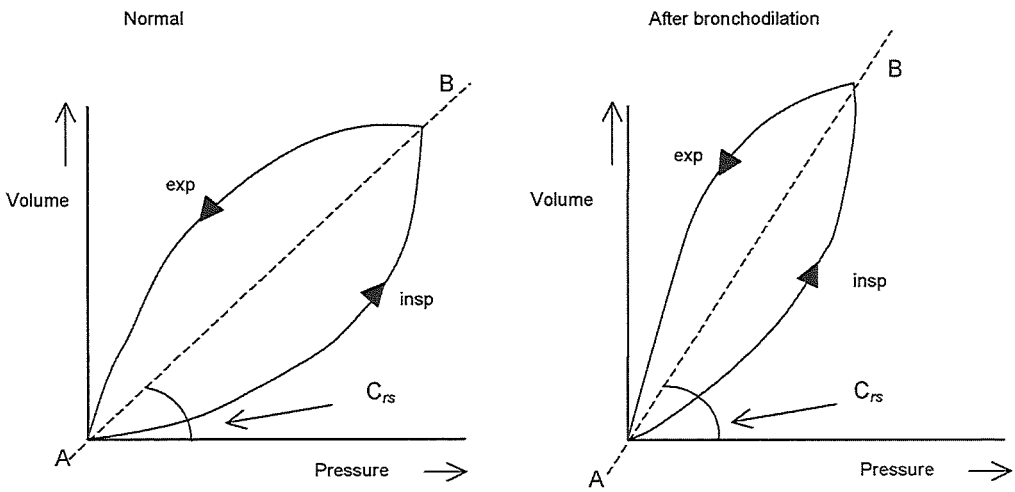

Figure 1. Pressure-volume diagrams. The left figure shows a normal pressure-volume diagram.The right figure shows a pressure-volume diagram in case of increased airway resistance. Insp: inspiration. Exp: expiration. C_{rs}: Compliance of the respiratory system. Mote the increase in compliance after bronchodilation

Another possible explanation could be that, according to guidelines, assessing $V'max_{FRC}$ after bronchodilation is done with the same jacket pressure as used before the administration (20). However, therapeutic interventions are known to influence airway characteristics (12). Moreover, $V'max_{FRC}$ is a lung function

parameter reflecting maximal flow, and not flow at a certain jacket pressure. Therefore, we believe that one should reassess the lowest pressure at which the highest flows are obtained, irrespective of the jacket pressure used before the therapeutic intervention. A future study should address the influence of the jacket pressure while measuring a bronchodilator response.

EXPLANATIONS FOR LACK OF EFFICACY OF β_2-AGONISTS ON CLINICAL PARAMETERS: There are several reasons why β_2-agonists do not always give an improvement of clinical parameters, such as a reduction in breathing frequency, diminished retractions and use of accessory respiratory muscles, in infants and toddlers with dyspnea. First, β_2-agonists increase the metabolic rate (21). In addition, salbutamol can give a drop of transcutaneously measured oxygen-saturation in wheezy infants (SaO_2) (22, 23). This is the result of β_2-agonists giving pulmonary vasodilatation and an increase in cardiac output. As a consequence, there is increasing perfusion of poorly ventilated lung units, resulting in a ventilation-perfusion mismatch, and thus giving or worsening hypoxaemia (23). It is not known in what percentage of infants with dyspnea, treatment with β_2-agonists results in hypoxaemia. One study of 111 children with acute severe asthma showed that 5% of the children became hypoxaemic after nebulised salbutamol (24). It can be concluded that there is evidence that some children may develop hypoxaemia after administration of β_2-agonists. Therefore, during a severe asthma attack, β_2-agonists should always be administered with oxygen (23). Finally, the lack of a positive effect of β_2-agonists on clinical parameters can of course also be the result of incorrect inhalation technique.

In summary, there is no need to exclude β_2-agonists as they are effective and safe in the treatment of reversible bronchoconstriction. However, in wheezy infants it is difficult to ascertain whether or not increased airway smooth muscle tone is an important contributor to the dyspnea. Therefore, we believe it is justified to consider a trial of β_2-agonists in the treatment of wheezy infants. If in infants with wheeze a treatment with β_2-agonists has no beneficial effects there is no further need to continue the treatment (2).

Several studies evaluated the role of inhaled steroids in the treatment of wheeze in infancy. However, data from these studies are non-conclusive. Only two studies evaluated the efficacy of fluticasone propionate (FP) using subjective outcome measures in young children (25, 26). To our knowledge, no study evaluated the efficacy of treatment with FP in infants with wheeze using objective parameters, next to symptom scores. Therefore, we assessed the effect of FP on lung function

and symptom scores in infants with persistent or recurrent wheeze (AIR-study) (Chapter 4). The second aim was to evaluate if infants with atopy and/or eczema respond better to FP treatment as compared with non-atopic infants.
We found that infants with recurrent or chronic wheeze did not show improved lung function after a 13 weeks treatment with fluticasone propionate 200 mg daily (FP200), inhaled from the Babyhaler. However, after 6 weeks of treatment, the infants treated with FP200 had a significant increase from baseline in symptom free days and a significant reduction in mean daily cough score, as compared with placebo. After 13 weeks of treatment, these findings were not different between the two groups.

Wildhaber and coworkers compared subjective measures (symptoms scored by the study physician and the child's mother) with objective measurements of $V'max_{FRC}$ and forced expiratory volumes (FEV_t) by means of the raised volume rapid thoracoabdominal compression (RVRTC) technique (27). Wheezy infants were studied during an acute exacerbation, and when the infant was asymptomatic. They found that mean FEV0.5 and FEV0.75, and not $V'max_{FRC}$, were significantly lower during an acute exacerbation as compared with the asymptomatic period. Moreover, mean FEV0.5 and FEV0.75, but not mean $V'max_{FRC}$, correlated with symptoms scored by the study physician. It was concluded that FEV_t measurement from the RVRTC technique correlated well with symptom scores and is therefore a feasible method to monitor obstructive lung disease (27). Another way to look at these findings is that $V'max_{FRC}$ did not correlate with symptoms, either scored by physician or parent. Moreover, FEV_t values did not correlate with symptoms scored by the parent. In other words, these lung function parameters correlate poorly with symptoms scored by parent(s). Therefore, the discrepancy in our study between effect of ICS treatment on lung function and improved symptom scores can be explained by poor correlation of lung function measurements and symptoms scored by the parent in wheezy infants (27).

In addition, FEV_t parameters from the RVRTC technique, and not $V'max_{FRC}$, could distinguish between a symptomatic and an asymptomatic period. Therefore, one could conclude that measurements of $V'max_{FRC}$ in our study were not sensitive enough to detect an effect, and that FEV_t measurement by RVRTC technique would have been better. However, the RVRTC technique remains nonstandardised with respect to equipment, methodology, or analysis, making comparisons of data collected in different centers difficult (28). Further evidence is required as to whether the more complicated approach of the

RVRTC technique will prove to be more sensitive than the tidal RTC technique in detecting changes in airway function or response to therapy in infants (29). If the RVRTC technique has proven to be beneficial over the tidal RTC technique, a new large randomized controlled trial studying the efficacy of ICS treatment in infants with wheeze should be conducted. This future study should also address the issue of correlation between lung function and symptom scores, scored by the parent(s).

The second aim of this study was to evaluate if infants with atopy and/or eczema respond better to fluticasone treatment as compared with non-atopic infants. However, treatment effect was not significantly modified by the presence of atopy or eczema. This is in contrast with a study by Chavasse and coworkers, who showed improvement of clinical symptoms in response to fluticasone in a group of wheezy infants with a history (personal or first degree relative) of atopy (26). In addition, Roorda and coworkers showed that preschool children (aged 12-47 months) with recurrent asthma symptoms showed the greatest response to FP treatment if they had frequent symptoms, a family history of asthma, or both (30). These studies suggest that atopic infants, or infants with a familial predisposition to atopy, are more likely to respond to ICS treatment as compared with non-atopic infants. Our study does not confirm this. An explanation could be that the lack of response of FP200 on lung function in our study, makes it more difficult to identify a subgroup in which treatment did have an effect on lung function.

Infants with Chronic Lung Disease

In chapter 5 we evaluated lung function during the first year of life in prematurely born infants of very low birth weight with chronic lung disease (CLD), in the era of surfactant therapy and high-frequency oscillation ventilation (HFOV). We concluded that these very low birth weight infants with CLD have decreased forced expiratory flows that worsen during the first year of life. Furthermore, initial treatment with HFOV was associated with a more favorable outcome of forced expiratory flows at 12 months corrected age.

To understand the implication of these findings, some background information is provided. In this discussion the terms bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) will be used interchangeably to refer to preterm infants with abnormal lung function and abnormal chest films late in their postnatal course (31).

The airways are well formed by 20 weeks gestation in the human. The distal lung parenchyma transitions from the canalicular to the saccular stage of lung development is at 23 to 24 weeks gestation; the time of earliest extrauterine viability. Alveoli begin to appear after 32 weeks gestation, but the alveolar stage of lung development in the human is from about 36 weeks gestation to 18 months postnatally. Approximately 30% of the adult number of alveoli have formed by term, but the majority of alveolarization occurs within 5 to 6 months of term birth (32, 33). If an infant is born preterm, lung development must proceed in the extrauterine environment while providing gas exchange. Northway and co-workers described bronchopulmonary dysplasia (BPD) in 1967, in a group of preterm infants, as severe lung injury resulting from mechanical ventilation and oxygen exposure (34). This 'old BPD' is characterized by persistent inflammation, fibrosis, and smooth muscle hypertrophy in the airways (35). With progress in neonatal care that includes antenal steroids, surfactant treatments and gentler ventilation strategies, large preterm infants seldom develop this 'old BPD', except for term infants that survive severe meconium aspiration or congenital diaphragmatic hernia after prolonged ventilation (31). However, the overall incidence of BPD has remained high as a result of the increased survival of extremely premature infants, who are most likely to develop BPD (36). Moreover, BPD is the most common complication of care infants born weighing less then 1 kg (37). Furthermore, BPD occurs frequently in infants weighing less then 1 kg who do not have initial lung disease after birth (38). Therefore, the traditional tandem of oxygen and barotrauma is not the major factor initiating much of the lung injury in very preterm infants nowadays (39). Hislop and coworkers concluded that ventilation of low birth weight infants yielded lungs with fewer alveoli (40). Husain and co-workers observed that infants dying of BPD in the recent era of surfactant treatment had fewer and larger alveoli with less striking fibrosis and inflammation that in the past (41). In addition, Jobe stated that the lungs of infants dying of BPD after several months of ventilation show minimal inflammation or fibrosis, but the lung seems to have an arrest in alveolar and vascular development corresponding to the gestation of the infant at delivery (39). These observations suggest that the major manifestation of lung injury of BPD in very preterm infants is interference with normal lung development (39). This interference with normal lung development can be reproduced in preterm animals. Albertine and coworkers studied surfactant treated preterm lambs by using routine ventilation strategies and minimal supplemental oxygen. They found a complete arrest of alveolar septation that resulted in fewer and larger alveoli (42). The animal models and clinical studies show that the 'new BPD' is mainly characterized by an arrest of lung develop-

ment, resulting in simplified lungs with increased alveolar sizes, decreased alveolar numbers and dysplastic pulmonary vasculature, and that the traditional indicators of injury are less evident (Table 1) (39, 43).

	Old BPD	New BPD
Mainly in infants with:	• Birth weight > 1kg • Birth weight < 1kg	• Gestational age > 30 wks • Gestational age < 30 wks
BPD result of:	• Baro- and chemotrauma as result of ventilation and oxygen	• Preterm birth with arrest in lung development. • Baro- and chemotrauma as result of ventilation and oxygen
Characteristics are:	• Persistent inflammation, fibrosis, and smooth muscle hypertrophy in the airways	• Arrest in lung development with fewer and larger alveoli • Less fibrosis and inflammation

Table 1. Differences between old bronchopulmonary dysplasia (BPD) and new BPD.

The statement that the 'new BPD' is mainly characterized by an arrest of lung development is confirmed by a number of reports demonstrating that preterm birth per se results in alterations in lung function that are most apparent in the early years of life and subsequently become less evident as children age (43-45). Hjalmarson and Sandberg compared lung function of 'normal' preterm infants measured at term with term infants (45). The preterms (mean gestational age 29.5 weeks) had dysfunction of terminal respiratory units and higher elastic recoil. The results are consistent with altered alveolarization after preterm birth. Because airway development precedes development of the alveoli and the pulmonary microvasculature, disturbances of the parenchymal development might be more severe than airway abnormalities after very preterm birth (43). Hoo and co-workers (46) showed that airway function may deteriorate during the first year of life in infants born prematurely in the absence of any neonatal disease or therapy. Preliminary findings from Hannover (47) reported a similar decrease in $V'max_{FRC}$ during the first year of life in 24 preterms with BPD. This provides further evidence regarding the importance of prematurity per se on subsequent lung growth. Our study showed that ventilated VLBW infants

who were oxygen dependent at 36 weeks gestation had abnormal forced expiratory flows that deteriorated during the first year of life (48). These results may represent the additive adverse effects of very preterm birth plus BPD at a time when the infants are growing rapidly (43). The effect of preterm birth is an arrest in lung development, where the disturbances of the parenchymal development might be more severe than airway abnormalities after very preterm birth (43). Therefore, the deterioration of forced expiratory flows during the first year of life in very preterm infants with or without BPD may indicate that these infants may be 'functionally growing out of their airways' (43, 49). When we reanalyzed our data using the more recent reference equations by Hoo and coworkers (50), no signficiant decline of function was observed in the 6 months of follow-up while the conclusions based on the data from the Hannover and London cohorts (46, 47) did not change. Hence, a period of 6 months may be too short to detect a decline when using reference equations based on length.

It can be concluded that there is growing evidence that reduced lung and airway function following preterm delivery may be related to developmental changes as much as to initial disease severity or to treatment effects. Improved antenatal care and avoidance of prematurity may be as important for future lung health as further improvements in neonatal ventilation strategies (43, 49). Therefore, future studies should concentrate on further follow-up of lung function from infancy into adulthood in preterm infants with or without BPD, and the collection of morphologic information about the lung parenchyma and airways of survivors of prematurity and BPD to be able to interpret physiologic tests of lung function. Tissue could be collected from children who have survived prematurity and BPD and who occasionally die from nonpulmonary causes (43).

In our study, the infants ventilated with high-frequency oscillation ventilation (HFOV) did not have decreased forced expiratory flows at 12 months of age, in contrast with conventionally ventilated infants (48). HFOV is thought to minimize airway injury by recruiting lung volume and then maintaining a higher than normal functional residual capacity and keeping the airways open during expiration (51). This could explain our finding that HFOV had abnormal but not deteriorating forced expiratory flows in contrast with conventional mechanical ventilation (CMV). However, this result is speculative since a limitation of our study was that ventilation strategy was not randomized. If HFOV is beneficial over CMV remains controversial, as again illustrated by two recently published

large trials, one showing modest benefit (52) and the other showing no benefit of HFOV over CMV (53). Differences in outcomes between HFOV and CMV may relate more to the way they are used and patient selection, than to the intrinsic characteristics of the devices (43).

Infants with a large airway abnormality

In chapter 6 we studied the diagnostic value of Infant Lung Function Testing (ILFT) in ruling out airway abnormalities in wheezy infants. We concluded that lung function testing in infants could not predict airway abnormalities in infants with airway obstruction, and can therefore not be used to select infants who should undergo bronchoscopy. However, flow limitation during tidal breathing was highly predictive of a large airway abnormality, but only half of the infants with large airway abnormalities had tidal flow limitation.

To our knowledge, this is the first study which addresses the added clinical value of lung function testing in the diagnosis of the infant with a respiratory problem (54). In our study, flow limitation during tidal breathing was highly predictive of a large airway abnormality. From a healthy symptom-free term cohort, we know that approximately 10% of the infants have flow limitation during tidal breathing at one month of age (55, 56). These tidal flow limited infants have a 7-fold increased risk for physician-diagnosed asthma at the age of 2 years (55). However, at 6 and 11 years these infants had increased airway responsiveness and reduced lung function, different from asthma, as compared with other cohort members (56). Whether these respiratory illnesses are based on central airway abnormalities remains to be elucidated, as bronchoscopic investigations were not carried out in these patients. However, our study in a selected group of infants suggests that tidal flow limitation in infancy is likely associated with a large airway abnormality.

It is known that the majority of infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life (8). Therefore, one could speculate that physician-diagnosed asthma at the age of 2 years is in fact persistent or recurrent wheeze due to a large airway abnormality. This hypothesis is supported by the finding from the same cohort that 'tidal flow limitation during infancy is associated with an increased risk for respiratory illnesses, possibly different from asthma, later in life' (56). Together with the conclusion from our study that tidal flow limitation in infancy is associated with a large airway abnormality, we state the hypothesis that flow limitation in healthy term symp-

tom-free infants is associated with central airway abnormalities, and not with asthma. If this hypothesis has proven to be correct, lung function testing could help to avoid long-term anti-asthma treatment in infants with a large airway abnormality (7). A future cohort study in healthy term symptom-free infants should ideally consider bronchoscopies in all infants. However, due to medical ethical reasons a bronchoscopy in healthy controls is not allowed.

In the introduction it is stated that $V'max_{FRC}$ is thought primarily to reflect airway mechanics upstream to the airway segment causing flow limitation, and therefore is a measure of peripheral airway function that is relatively independent of upper airway resistance (29, 54, 57). Our study showed that $V'max_{FRC}$ may also reflect central airflow limitation in infants with central airway abnormalities, leading to tidal flow limitation. This suggests that the flow-limiting segment in malacia or stenosis remains in the central airways throughout expiration, and not in the peripheral airways. The same phenomenon was seen by Tepper and coworkers (58). They studied three infants with three different lesions of the central airways (vascular ring, congenital tracheal stenosis, subglottic polyp). Preoperatively, all three demonstrated severe flow limitation with a relatively constant forced expiratory flow over the tidal volume range. Postoperatively the expiratory flow-volume curves changed to a normal convex shape and $V'max_{FRC}$ returned to normal (58). This could mean that $V'max_{FRC}$ is not independent of the upper airway resistance. Possibly, $V'max_{FRC}$ reflects peripheral airway function only in the absence of a large airway resistance in the upper airways as tidal flow limitation can also be the result of severe peripheral airway obstruction. Nonetheless, we believe that in the presence of a large airway abnormality, such as a vascular ring, airway malacia or tracheal stenosis, $V'max_{FRC}$ reflects central airflow limitation. This means that especially in the case of tidal flow limitation, one should be cautious interpreting $V'max_{FRC}$.

Future research, as proposed in the previous paragraph, should concentrate on determining the association between tidal flow limitation and large airway abnormalities as diagnosed by bronchoscopy. In addition, larger studies are needed to study the effect of operative corrections of large airway abnormalities on lung function, and especially on the presence of tidal flow limitation.

Infants with respiratory failure treated with ECMO

In chapter 7 we evaluated lung function during the first year of life in infants following ECMO support. Investigation of lung function of survivors of extra-

corporeal membrane oxygenation (ECMO) is essential to evaluate whether or not ECMO gives a survival advantage. To our knowledge, no study evaluated lung function longitudinally during the first year of life in ECMO survivors. Therefore, we aimed to evaluate lung function during the first year of life in infants following ECMO support. We found that during the first year of life, these infants who received ECMO support have normal lung volumes and normal expiratory flow that did not worsen upon follow-up. These data suggest limited effects of ECMO on lung function development.

Fifty-five percent of the infants studied received ECMO for meconium aspiration syndrome (MAS). This large incidence of MAS in our study is in contrast with a lower incidence of infants with MAS requiring ECMO in the United States. This is explained by the finding that in the USA, MAS decreased nearly four-fold between 1990 and 1998 (59). Next to an increased cesarean delivery rate, the most important factor in reducing the incidence of MAS was a 33% decrease in births after more than 41 weeks gestational age (GA) with a reciprocal 33% increase in births 38-39 weeks GA (59). Therefore, follow-up of a large group of infants who received ECMO for MAS will be more difficult to conduct in the United States.

We found higher long volumes at 6 and 12 months in the infants who received ECMO for congenital diaphragmatic hernia (CDH), as compared with normal values or with the infants who received ECMO for meconium aspiration syndrome (MAS). However, these differences were not statistically significant, probably due to lack of power. Other studies have found low or normal lung volumes in infants following ECMO for CDH (60, 61). The achievement of a normal lung volume later in infancy (62) may be masking alveolar distension and destructive emphysema (63, 64). Nagaya and co-workers studied lung volume and pulmonary perfusion in infants following surgical repair of CDH and ECMO treatment (61). They found that these infants had low lung volumes (61% of contra-lateral lung volume), which increased during follow-up (88% of contra-lateral lung volume). In contrast, the lung perfusion of the affected side had not increased in most cases or decreased to below the initial value. It was concluded that the lung of the affected side has little ability to develop arterial branches and that enlargement of lung volume may depend on overexpansion or emphysematous change, rather than cellular growth (61). These findings are supported by Muratore and colleagues, who systematically performed ventilation-perfusion scans in a structured follow-up of CDH infants after ECMO support (65). They showed the presence of a ventilation-perfusion mismatch on

subsequent pulmonary ventilation-perfusion examinations. These data suggest that the affected lung has little ability to develop arterial branches or capillaries. Since capillary and alveolar proliferation are linked (66), alveolar development might be impaired in the affected lung of infants with CDH. In contrast, a morphological study of the lungs of 21 infants with CDH who died, showed that lung growth does occur postnatally at the alveolar level after CDH repair. In addition, postnatal vascular remodeling results in larger and less muscular arteries (67). Possibly, with the introduction of ECMO more severe cases of CDH have survived, with consequently diminished hypoplastic lungs. We believe that the increase in lung volume is most likely the result of hyperinflation of existing alveoli resulting in a emphysematous lung. Moreover, we speculate that there is absence of alveolar catch-up growth of the hypoplastic lung resulting in more severe alveolar distension and destructive emphysema. Further follow-up of lung function in infants after CDH repair must be performed to clarify the presence and the role of increased lung volume.

Conclusion

The primary objectives of the studies in this thesis were to evaluate lung function in infants with several respiratory disorders and to study the effect of treatment with inhaled steroids in infants with recurrent wheeze. Secondary objectives were to study the clinical value of lung function testing in the management of the infant with a respiratory problem, and to study the relationship between lung function and patient characteristics.

With chapter 3 (β_2 -agonists infants with wheeze and airway malacia), chapter 4 (efficacy of inhaled steroids in wheezy infants), chapter 5 (lung function in infants with chronic lung disease of prematurity) and chapter 7 (lung function in infants after ECMO support) we achieved the primary goal of the thesis. With chapter 6 (ILFT for ruling out airway malacia) we achieved the second aim of studying the clinical value of lung function testing in the management of the infant with a respiratory problem. The correlation of patient characteristics and lung function has been studied in chapter 4, 5 and 7.

We believe that the studies of infant lung function measurements presented in this thesis have provided more insight in the pathophysiology of several respiratory disorders in infancy and have contributed to the clinical management of infants with a respiratory problem.

Directions for future research

Many chronic respiratory disorders that originate in infancy have not been studied in great extend. Infant lung function studies may provide early insight in the extent of the functional limiations that are associated with those disorders, and may serve as an aid in modifying or initiating treatment of these infants. Two examples of categories of patients who deserve a structured follow-up are provided.

Infants with Cystic Fibrosis

In infants with cystic fibrosis (CF), measurement of lung function may be even more relevant than measurements in adulthood, as inflammation and infection may develop early in life and may be present without clinical signs (29, 68). Moreover, any damage sustained during these periods of rapid lung growth and development is more likely to have long-term adverse effects (29). Nonetheless, the natural course of pulmonary involvement in infants with CF before infection occurs and disease becomes clinically evident, remains poorly understood (29). Although serial measurements of lung function are well known to be far more valuable than a single assessment(69), very little longitudinal data are available for infants due to difficulties in performing measurements frequently (70, 71). Therefore we started a structured follow-up of lung function in infants with CF on October 1st 2003. Lung function will be related to patient characteristics, such as mode of presentation, CF-genotype, number of hospitalizations for respiratory causes, use of antibiotics, bacterial cultures, prenatal and postnatal tobacco smoke exposure.

Infants following repair of esophageal atresia and tracheoeosophagal fistula

In the introduction we state that children following repair of esophageal atresia and tracheoesophageal fistula (OA-TOF) often have variable respiratory and gastro-intestinal symptoms, mainly during the first 3 years of life(72, 73), and are known to have lung function abnormalities (73-75). It is not clear whether respiratory symptoms and abnormal lung function is in related with gastro-esophageal complications (74-76). Possibly, lung function measurements during infancy can elucidate this question as symptoms are predominantly present during the first 3 years of life. Unfortunately, there are no structured follow-up studies of lung function in infancy after repair of OA-TOF. Abnormal pulmonary function tests may result from reduced lung growth after surgery (73) and/or may reflect variable respiratory and/or gastro-intestinal symptoms.

Moreover, the effect of interventions can be studied more thoroughly using follow-up studies. In addition, tracheomalacia is associated with OA-TOF repair (77). It is not clear to what extent the flow-limiting segment of the tracheomalacia influences lung function. A structured follow-up of lung function in infants following OA-TOF repair, which accounts for symptoms, interventions and possibly bronchoscopic evaluation of tracheomalacia, could provide more insight in the pathophysiology following OA-TOF repair.

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NEDERLANDSE SAMENVATTING

Longfunctieonderzoek bij zuigelingen en peuters wordt sinds ruim 50 jaar uitgevoerd. Het is echter niet duidelijk wat longfunctie onderzoek gedurende de eerste 2 levensjaren kan bijdragen aan het klinisch handelen (1). De meeste artikelen over longfunctieonderzoek op deze leeftijd zijn uitgevoerd in het kader van wetenschappelijke vraagstellingen, met name methodologie van longfunctie en fysiologisch en pathologisch onderzoek. Er is maar een klein aantal studies dat longfunctieonderzoek bij zuigelingen en peuters heeft verricht voor klinische toepassingen, zoals het vervolgen van bepaalde respiratoire ziektebeelden of behandeleffecten (1). Er zijn geen studies gepubliceerd die de klinische toegevoegde waarde van het longfunctieonderzoek hebben onderzocht bij de behandeling van een jong kind met een respiratoir probleem (1).
De primaire doelstellingen van het onderzoek dat beschreven wordt in dit proefschrift waren om met behulp van longfunctiemetingen: A) het beloop van de longfunctie van zuigelingen met verschillende ernstige respiratoire aandoeningen te vervolgen, en B) de effectiviteit van de behandeling met inhalatiesteroïden bij zuigelingen en peuters met piepende ademhaling te evalueren. Secundaire doelstelling was het onderzoeken van de relatie tussen longfunctie en patiëntkarakteristieken.

Hoofdstuk 1 geeft een samenvatting van de literatuur met betrekking tot de methodologie van het longfunctieonderzoek bij jonge kinderen, alsmede een samenvatting van klinische studies van longfunctieonderzoek bij zuigelingen en peuters.

Hoofdstuk 2 bevat een algemene inleiding en de doelstellingen van het proefschrift.

In hoofdstuk 3 is het effect van bronchusverwijders (β_2-agonisten) op de longfunctie (luchtwegdoorgankelijkheid) onderzocht bij jonge kinderen met piepende ademhaling of een aangeboren afwijking van de luchtpijp (malacie). Tevens is onderzocht of het effect van de β_2-agonist op de luchtwegdoorgankelijkheid anders was in de groep met malacie, in vergelijking met de groep met piepende ademhaling. Wij vonden dat binnen de groep met piepende ademhaling, er een significante afname was van de luchtwegdoorgankelijkheid na behandeling met β_2-agonisten. Een mogelijke verklaring voor deze bevinding is

dat de luchtwegdoorgankelijkheid van kinderen met malacie voorafgaand aan bronchusverwijding al significant lager was.

In hoofdstuk 4 onderzochten we het effect van inhalatiesteroïden op de longfunctie bij jonge kinderen (tot 2 jaar) met terugkerende of chronische symptomen van piepende ademhaling middels een dubbelblinde gerandomiseerde placebo gecontroleerde studie (AIR-studie). De hypothese was dat een 3 maanden durende behandeling met fluticason propionaat 200 mg per dag (FP200) een verbetering laat zien van luchtwegdoorgankelijkheid met een afname van respiratoire symptomen, ten opzichte van placebo. Een tweede doelstelling was om te evalueren of piepende kinderen die bovendien atopie en/of eczeem hebben, en daardoor een grotere kans hebben op astma, beter reageren op behandeling met FP200 dan kinderen zonder atopie en/of eczeem. Wij vonden geen verbetering van de longfunctie na 3 maanden behandeling met FP200 bij kinderen met terugkerende of chronische symptomen van piepende ademhaling. Echter, na 6 weken behandeling hadden de kinderen in de FP200 groep significant meer symptoomvrije dagen en een significante afname van hoestklachten, in vergelijking met de placebogroep. Na 3 maanden behandeling waren deze verschillen tussen de beide groepen verdwenen. Kinderen met atopie en/of eczeem reageerden niet beter op de behandeling dan kinderen zonder atopie. Een verklaring voor de afwezigheid van een duidelijk effect van FP200 op de longfunctie kan zijn dat er bij het grootste gedeelte van de jonge kinderen met piepende ademhaling geen sprake is van astma, maar van een tijdelijk verminderde luchtwegdoorgankelijkheid ten gevolge van aangeboren nauwe luchtwegen (2). Onze studie bevestigt wel bevindingen van andere studies (3, 4) dat behandeling met FP200 een afname geeft van de respiratoire symptomen bij jonge kinderen met piepende ademhaling.

In hoofdstuk 5 evalueerden wij de longfunctie van prematuur geboren zuigelingen met een zeer laag geboortegewicht die als gevolg van de behandeling longschade hebben opgelopen (bronchopulmonale dysplasie, BPD). Wij vonden dat deze zuigelingen met BPD een verminderde luchtwegdoorgankelijkheid hebben, welke verslechterde gedurende het eerste levensjaar. Tevens vonden wij dat initiële beademing met high-frequency oscillation (HFOV) was geassocieerd met betere luchtwegdoorgankelijkheid op de leeftijd van 12 maanden, ten opzichte van de kinderen behandeld met conventionele beademing. Wij veronderstellen dat de afname van luchtwegdoorgankelijkheid het gevolg is van een abnormale functionele en/of anatomische ontwikkeling van de luchtwegen. Of dit het gevolg is van de preterme geboorte, de mechanische

beademing, of van beide, blijft onduidelijk.
In het addendum bij hoofdstuk 5 hebben we de gegevens van hoofdstuk 5 opnieuw geanalyseerd met recente geslachtsspecifieke referentiewaarden. Bij de nieuwe analyse blijkt dat de luchtwegdoorgankelijkheid niet veranderd tussen de gecorrigeerde leeftijd van 6 en 12 maanden bij zuigelingen met BPD. Tevens laten de zuigelingen die initieel met HFOV zijn beademd een significante toename zien van de luchtwegdoorgankelijkheid gedurende het eerste levensjaar. Uit deze gegevens kan geconcludeerd worden dat de keuze van referentiewaarden het resultaat significant kan beïnvloeden en dat het effect van het type initiële beademing mogelijk nog meer uitgesproken is.

In hoofdstuk 6 bestudeerden wij de diagnostische waarde van longfunctieonderzoek bij jonge kinderen met luchtwegmalacie. Wij vonden dat longfunctiemetingen een lage negatief voorspellende waarde en een lage sensitiviteit hadden voor de diagnose malacie. Luchtstroombelemmering tijdens rustademhaling was 100% voorspellend voor de aanwezigheid van een malacie, maar werd bij slechts de helft van de kinderen met een malacie gevonden. Wij concludeerden dat longfunctieonderzoek bij jonge kinderen niet geschikt was om een luchtwegmalacie uit te sluiten en niet kan worden gebruikt om te bepalen of een kind een bronchoscopie moet ondergaan.
In hoofdstuk 7 hebben wij de longfunctie geëvalueerd van zuigelingen na behandeling met extracorporele membraan oxygenatie (ECMO). Onze gegevens lieten zien dat deze zuigelingen gedurende het eerste levensjaar een normaal longvolume en een normale luchtwegdoorgankelijkheid hebben, welke niet verslechtert. Deze gegevens suggereren een beperkte invloed van ECMO op de longontwikkeling. De subgroep van zuigelingen die ECMO hebben ondergaan als gevolg van een aangeboren afwijking van het middenrif (congenitale hernia diafragmatica) liet een trend zien van een verhoogd longvolume ten opzichte van de normaal waarden.

De studies in dit proefschrift laten zien dat het onderzoek naar de longfunctie bij jonge kinderen zich, na een fase van vooral methodologische vraagstellingen, inmiddels bezighoudt met klinische vraagstellingen. Deze verschuiving is voornamelijk het gevolg van publicaties van richtlijnen voor longfunctieonderzoek bij jonge kinderen en standaardisatie van apparatuur door de European Respiratory Society en de American Thoracic Society (ERS/ATS) (5-8). Dankzij deze richtlijnen zijn normaalwaarden gepubliceerd voor de verschillende longfunctietechnieken en is het nu mogelijk om gegevens van verschillende longfunctie laboratoria met elkaar te vergelijken. Bovendien is

longfunctieapparatuur voor zuigelingen nu commercieel verkrijgbaar en deze voldoet aan de eisen van de ERS/ATS. Met deze ontwikkelingen is aan de voorwaarden voldaan om longfunctie onderzoek bij jonge kinderen op grote schaal in de kliniek toe te passen, bijvoorbeeld in de vorm van multi-centrische therapie studies (9).
Echter, de hoge aanschaf kosten van de apparatuur, de noodzaak om personeel speciaal op te leiden en het feit dat meeste metingen onder sedatie moeten plaatsvinden, betekenen dat longfunctieonderzoek bij jonge kinderen beperkt zal blijven tot de grotere, veelal academische, centra. De uitdaging voor de toekomst zal zijn om klinisch relevante longfunctieonderzoeken te ontwikkelen die toepasbaar zijn in de algemene praktijk. Ideaal is wanneer deze onderzoeken goedkoop zijn, eenvoudig uitvoerbaar en toegepast kunnen worden zonder sedatie. Wanneer aan deze voorwaarden is voldaan, wordt het mogelijk dat longfunctie onderzoek bij jonge kinderen zich ontwikkelt van een geavanceerde derdelijnsvoorziening naar een routinetest voor de algemene praktijk (9).

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Dankwoord

Vier en half jaar geleden kon ik me niet voorstellen dat ik nu ben aangekomen bij het schrijven van het dankwoord. Mogelijk het enige hoofdstuk van mijn proefschrift dat echt gelezen wordt. De eer die dit hoofdstuk toekomt is buiten iedere proportie gezien het feit dat ik verhoudingsgewijs hier het minste tijd aan heb besteed. Dit is tevens het enige hoofdstuk dat ik echt alleen heb geschreven. Voor de andere hoofdstukken heb ik onmisbare hulp gehad van een groot aantal mensen. Een aantal wil ik graag bij deze bedanken:

Prof.dr. J.C. de Jongste, beste Johan en Dr. P.J.F.M. Merkus, beste Peter. Een gezamenlijk dankwoord voor mijn promotor en copromotor aangezien zij de afgelopen jaren het team vormden waarmee ik mocht werken. Normaal is het gras groener bij de buren, maar ik ben ervan overtuigd dat ik het niet beter had kunnen treffen. De ontspannen sfeer en de vrijheid die jullie mij hebben gegeven, hebben geresulteerd dat het mijn eigen onderzoek is geworden. Johan, dank voor je snelle correcties en je altijd eerlijke mening. Ik stond daar niet altijd op te wachten, maar helaas had je wel altijd gelijk. Peter, wat moet het heerlijk idee zijn dat er nu 2 mensen in Nederland zijn die plaatjes in Fig.P kunnen maken.

Het onderzoek was niet mogelijk geweest zonder de financiële steun van GlaxoSmithKline, Nederland. Ik wil GlaxoSmithKline graag hartelijk bedanken voor de volledige sponsoring van het gehele onderzoek, inclusief de 3 maanden uitloop, en de genereuze bijdrage aan de drukkosten van het proefschrift. Dankzij de wetenschappelijke vrijheid die jullie ons hebben gegeven, zijn wij in staat gesteld om het longfunctie onderzoek bij baby's in een klinische context te plaatsen. Niet alleen bij kinderen met wheeze, maar ook bij kinderen met anderen respiratoire aandoeningen. Met name Niek Vermue en Miranda de Vries wil graag persoonlijk bedanken voor hun betrokkenheid en ondersteuning tijdens de afgelopen jaren.

Prof.dr. H.A. Büller, Prof.dr. D. Tibboel en Prof.dr. W.M.C. van Aalderen wil ik bedanken voor de bereidheid om in de kleine commissie zitting te nemen en voor de beoordeling van het manuscript. Prof. M. Gappa, Prof.dr. J.W. Wladimiroff, Prof.dr. J.A.M. Raaijmakers en Prof.dr. J.B. van Goudoever wil ik bedanken voor hun deelname aan de grote commissie.

Mijn paranimfen, Ymke Hofhuis en Toine van Buul. Lieve Ymke, naast broer en zus en maatjes zijn we de laatste jaren ook huisgenoten geworden. Ik ben blij dat we zo dicht bij elkaar wonen en dat we zo close zijn. Dank je wel voor je wie je bent en voor alle keren dat ik mocht aanschuiven bij het eten. Succes met de afronding van jouw proefschrift, een hele prestatie in combinatie met het moederschap. Ik ben trots op je. Toine, ik heb het al eens eerder gezegd maar de grens tussen vriendschap en broederschap is bij ons vervaagd. Wat is het mooi dat we zoveel bijzondere momenten delen. Dank jullie wel voor het er altijd voor me zijn.

Els van der Wiel en Eveline Nieuwhof. Mijn linker- èn rechterhand, en af en toe mijn linker- èn rechterhersenhelft. Moeder Ganzen in het kwadraat. Els, buiten het feit dat jij mij alles hebt geleerd over longfunctie onderzoek bij baby's, wil ik je met name bedanken voor je onvoorwaardelijke steun, je kritische blik en je humor. Eveline, met je geen-woorden-maar-daden mentaliteit was jij een onmisbaar tegenwicht voor Els en mij. Dank jullie wel voor jullie flexibiliteit als alle metingen weer eens werden verschoven. Ik hoop dat jullie nu eindelijk eens vaste dagen hebben. Lieve meisjes, hoe moet het nu verder met mij in de grote wereld zonder jullie? Het is koud onder jullie vleugels vandaan.

Mw. Dr. M.W.H. Pijnenburg -Koenen, kinderlongarts, representative of the northern hemisphere, lieve Marielle. Mijn allerliefste kamergenoot. Met wie moet ik nu de wekelijkse perikelen van het County Cook General Hospital bespreken? Net als Dr. Ross en Dr. Benton ga ik het nu ook elders zoeken. Als ik Carter was, dan was jij Abby. Ik zal je missen.

Dr. H.A.W.M. Tiddens, beste Harm. De aanstichter van dit alles. Eigenlijk is het allemaal jouw schuld dat ik hier nu sta. Je enthousiasme prikkelt, bewondert en soms overrompelt. Saai is het in ieder geval nooit.

Manon Hanekamp. Lieve Manon, het was een feest om met jou te mogen werken. Wellicht dat we later wel eens samen dienst moeten draaien, als we groot en sterk zijn. Wanneer gaan we weer naar Cinema Paradiso (Sgropinootje of 3)?

Net als velen voor mij ben ook ik ervan overtuigd dat de longafdeling de leukste afdeling van het Sophia is. Samen met mijn stage periode als student ken ik deze afdeling vanaf 1997. Velen hebben bijgedragen aan de leuke en constructieve sfeer op de afdeling: Prof.dr. H.J. Neijens, José Espsito, Karen Corver, Rijn Jöbsis, Maartje ten Berge, Aafke, Astrid, Edith, Saskia, Sylvia, Annelies,

Anita, Simone, Margriet, Monique, Sonja, Marianne, Marion, Marieke, Maaike, Sandra, Tjitske. Een bijzonder 'dank-je-wel' voor Irma Beckers. Irma, dank je wel voor alle correcties, hulp, vertalingen, drop en gezelligheid, maar vooral je onovertroffen brownies. Ik hoop dat niemand ooit het record 'brownies eten' verbetert.

Dat ik zelden tot nooit mee ging lunchen heeft ertoe bijgedragen dat ik reeds vorig jaar op de lijst van oud-onderzoekers stond en dat ik vele huidige collega-onderzoekers niet ken. Desondanks wil ik enkelen in het bijzonder bedanken voor de gezelligheid voor of na de lunch, tijdens de Ropa-run of gewoon in WP; Karen, José, Carmelo, Ester Klein, Pieter, Edwin, Daphne, Saskia, Hestien, Venje, Nicolette, Geert, Jessie en Sophie. Laurens, je hebt gelijk gekregen: er is nooit meer een echte mannenkamer geweest en die zal er ook nooit meer komen. Hettie, dank je wel voor het 'mij over de streep trekken'. Wat een ogenschijnlijk onschuldige opmerking teweeg kan brengen.

Dr. W.C.J. Hop, beste Wim. Je heldere uitleg en de gezellige middagen maakten dat ik statistiek nog leuk ging vinden ook. Het shagjes roken op de parkeerplaats bij Glaxo blijft een prachtige herinnering met een hoog middelbare school gevoel.

Drs. G. Brinkhorst, beste Govert. Dank zij al het voorbereidende werk verricht door jou en Els was alle apparatuur klaar om met het babylongfunctie onderzoek de stap naar het klinisch onderzoek te zetten. We zien elkaar in Alkmaar.

Arno van Vliet en Ed Hoorn. De 'trouble shooters'! Regelmatig heb ik vlak voor of zelfs tijdens een meting op jullie terug moeten vallen. Altijd stonden jullie klaar als de apparatuur ons weer eens in de steek liet. Dank jullie wel voor jullie flexibiliteit en hulp.

Alle ouders en kinderen die afgelopen jaren hebben meegedaan aan de verschillende studies.

Alle artsen die hebben meegewerkt aan het onderzoek: Dr. W.A. Marianne Huysman, Drs. F.J. Smit, Drs. F.G.A. Versteegh, Dr. E.H.G. van Leer, Dr. P.J. van der Straaten, Drs. R. Schornagel, Mw. Dr. A.A.P.H. Vaessen-Verberne, Drs. R.M. Colombijn, Mw. Drs. M.C.W. Jacobs, Mw. Drs. M.J. Affourtit, en in het bijzonder Lianne Abels, dankzij wie vele kinderen hebben meegedaan aan de AIR-studie.

Niels Bekking, ik vind het geweldig dat jij mijn proefschrift wilt uitgeven. Dank je wel voor je hulp en begeleiding bij het verwezenlijken van mijn proefschrift. Nicole Maurer, dank je wel voor het maken van de mooiste plaatjes in mijn proefschrift.

Mijn ouders, lieve papa en mama. Dank jullie voor de onvoorwaardelijke steun, de stok achter de deur en onbegrensde mogelijkheden die jullie mij hebben gegeven. Mama, ik weet dat je er bij bent. Ik hou van jullie. Kus.

Oma Miesje. Ik weet dat ik veel voor jou beteken, maar je wilt niet weten hoeveel jij voor mij betekent.

Lieve Hester. We hadden wat omwegen nodig, maar wat ben ik blij dat we elkaar weer zijn tegengekomen. Je bent mijn allerliefste. Ik hou van je.

Curriculum Vitae

Ward Hofhuis was born in Rotterdam, on May 13th, 1971. He passed his secondary school exam (VWO) at the 'Sint Maartenscollege' in Maastricht in 1991. In 1992 he started his medical training at the Medical Faculty of the University of Amsterdam. During his study he had clinical trainings in Wilmington, University of North Carolina, U.S.A. (Dr. E. van Rens), and in Genova, Istituto 'G. Gaslini', Clinica Pediatrica dell' Universita, Italy (Dr. L. Romano). He also participated in a research project at the department of Pediatric Pulmonology of the Sophia Children's Hospital, Erasmus Medical Center, University of Rotterdam under supervision of Dr. H.A.W.M. Tiddens (Prof.dr. J.C. de Jongste). After obtaining his medical degree in 1999 he started a research fellowship at this department under supervision of Dr. P.J.F.M Merkus and Prof. dr. J.C. de Jongste. The research performed during this period is presented in this thesis. In January 2004 he started working as a resident at the department of Gynaecology and Obstetrics at the Sint Lucas Andreas Hospital, Amsterdam (Prof.dr. F Scheele). In October 2004 he will commence his specialist training in Gynaecology and Obstetrics at the University of Amsterdam (Prof.dr. O.P. Bleker), starting at the Medical Center Alkmaar (Dr. Y.M. van Kasteren).

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Abbreviations

ATS	American thoracic society
BF	Breathing frequency
BTPS	Body temperature and pressure saturated
BPD	Bronchopulmonay dysplasia
CF	Cystic fibrosis
CI	Confidence interval
CLD	Chronic lung disease
$C_{L,dyn}$	Dynamic lung compliance
cm	Centimeters
CMV	Conventional mechanical ventilation
CV	Coefficient of variation
C_{rs}	Compliance of the total respiratory system
E	Elastance
ECMO	Extracorporeal membrane oxygenation
EEL	End expiratory level
EEV	Elastic equilibrium volume
FE_{NO}	Fractional exhaled nitric oxide concentration
FEV_1	Forced expired volume in 1 second
FEV_t	Forced expired volume in a given time (forced expiratory volume/time)
FRC	Functional residual capacity
FRC_{He}	Functional residual capacity, measured using Helium wash out
FRC_{N2}	Functional residual capacity, measured using nitrogen (N2) wash out.
FRC_p	Functional residual capacity, measured using a whole body plethysmograph
FVC	Forced vital capacity
HBIR	Hering-Breuer inflation reflex
HFOV	High-frequency oscillation ventilation
i.e.	It est. Meaning 'that is'.
ILFT	Infant lung function testing
iNOS	Inducible nitric oxide synthase enzyme
kg	Kilogram
L	Crown heel length in centimeters
LN	Natural logaritme
MEF_{50}	Maximal expiratory flow at 50% FVC

MEF_{25}	Maximal expiratory flow at 25% FVC
mL	mililiters
MOT	Multiple occlusion technique
NO	Nitric oxide
NOS	Nitric oxide synthase enzymes
P_A	Alveolar pressure
P_{ao}	Pressure at the airway opening
P_B	Barometric pressure
P_{el}	Elastic pressure of the lungs
PEF	Peak expiratory flow
ppb	Parts per billion
P_{pl}	Pleural pressure
P_{res}	Resistive pressure of the lungs
R_{aw}	Airway resistance
R_{int}	Resistance of the airways measured by interrupter technique
R_L	Lung resistance (lung tissues and airways combined).
R_{rs}	Resistance of the respiratory system (chest wall, lung tissues and airways)
RSD	Residual standard deviation
RTC	Rapid thoracicabdominal compression
RVRTC	Raised volume rapid thoracicabdominal compression
SaO_2	Transcutaneous oxygen saturation
SBT	Single-breath technique
SD	Standard deviation
t_E	Total expiratory time
TGV	Thoracic gas volume
TLC	Total lung capacity
t_{PTEF}	time to reach peak expiratory flow
t_{PTEF}/t_E	time to reach peak expiratory flow as a proportion of total expiratory time
τ_{rs}	Slope of the flow-volume relationship during passive expiration
TV	Tidal volume
V	Volume
V'	Flow
$V'max_{FRC}$	Maximal flow at functional residual capacity
VLBW	Very low birth weight
W	Bodyweight in kilogram