A Critical Evaluation Of Respiratory Function Testing
In Spontaneously Breathing And Ventilated Infants

A thesis submitted by
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for the Degree of Doctor of Philosophy

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Abstract
At the inception of this thesis in 1991, there was increasing interest in infant respiratory function measurements following the development of simpler methods of testing including the tidal breathing parameter \( t_{\text{PTFE}}:t_E \), passive respiratory mechanics using the occlusion techniques and the rapid thoraco-abdominal compression technique (RTC). In addition, there were technological advances including the introduction of automated equipment for use in intensive care. The main aim of this thesis was to evaluate critically these recent advances.

Factors influencing the variability of \( t_{\text{PTFE}}:t_E \) were assessed. \( t_{\text{PTFE}}:t_E \) was higher with greater within-subject variability during the first few weeks of life. Twenty to fifty breaths are needed to obtain a representative value. Suggestions that \( t_{\text{PTFE}}:t_E \) could be measured using uncalibrated respiratory inductance plethysmography were not confirmed. Only a weak association between \( t_{\text{PTFE}}:t_E \) and established plethysmographic measures of airway function could be demonstrated.

Passive respiratory mechanics measurements had a higher failure rate than plethysmography. An extremely variable relationship between respiratory and airway resistance was observed within infants although both were significantly higher in infants with a history of wheeze.

The RTC proved useful in detecting airway disease in symptomatic infants. In contrast to passive respiratory mechanics, the RTC is more satisfactory in the presence of airway disease than in healthy infants. The method continues to be refined and is the most promising of the recent developments.

Assessments of automated measurement systems show the need to establish standards and ensure awareness of technical limitations of the equipment and the underlying assumptions of the measurement methods. The display of flow, volume and pressure data may be all that is routinely possible in the clinical management of unparalysed ventilated infants. Technological advances in the measurement of dynamic mechanics, including the development of catheter tipped microtransducers, may lead to the resurgence of dynamic mechanics measurements for research studies in this population.
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Symbols, abbreviations and units

The symbols, abbreviations and units used in this thesis are based on the ATS-ERS Working Party on "Infant Pulmonary Function Testing" recommendations. The main abbreviations used and conversion factors between S.I. (System International) and traditional units are summarised in the table below.

### Table of abbreviations and conversion factors

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<th>Abbreviation</th>
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<tbody>
<tr>
<td>A</td>
<td>alveolar</td>
<td>E</td>
<td>elastance</td>
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<tr>
<td>AB</td>
<td>abdomen</td>
<td>E, exp</td>
<td>expiratory</td>
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<tr>
<td>ao</td>
<td>airway opening</td>
<td>EE</td>
<td>end expiratory</td>
</tr>
<tr>
<td>aw</td>
<td>airway(s)</td>
<td>EEL</td>
<td>end expiratory level</td>
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<tr>
<td>B</td>
<td>barometric</td>
<td>el</td>
<td>elastic</td>
</tr>
<tr>
<td>BTPS</td>
<td>body temperature, barometric pressure and saturated with water vapour</td>
<td>F</td>
<td>female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f</td>
<td>frequency</td>
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<tr>
<td></td>
<td></td>
<td>$F_{\text{i},\text{CO}_2}$</td>
<td>fractional inspired carbon dioxide concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F_{\text{i},\text{O}_2}$</td>
<td>fractional inspired oxygen concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$f_r$</td>
<td>respiratory frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEV$_t$</td>
<td>forced expiratory volume in $t$ seconds</td>
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<td></td>
<td></td>
<td>FRC</td>
<td>functional residual capacity</td>
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<th>abbreviation</th>
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<td>FVC</td>
<td>forced expiratory vital capacity</td>
<td>m</td>
<td>metre</td>
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<tr>
<td>G</td>
<td>conductance</td>
<td>max</td>
<td>maximal</td>
</tr>
<tr>
<td></td>
<td>(1/r resistance)</td>
<td>min^-1</td>
<td>per minute</td>
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<tr>
<td>G_{aw}</td>
<td>airway conductance</td>
<td>MIT</td>
<td>multiple interruption</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
<td>ml</td>
<td>millilitre</td>
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<tr>
<td>GA</td>
<td>gestational age</td>
<td>mL</td>
<td>millilitre</td>
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<td>HBIR</td>
<td>Hering-Breuer Inflation reflex</td>
<td>MLR</td>
<td>multiple linear</td>
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<tr>
<td>Hz</td>
<td>hertz</td>
<td>mm</td>
<td>millimetre</td>
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<tr>
<td>I, insp</td>
<td>inspiratory</td>
<td>mmHg</td>
<td>millimetre of mercury</td>
</tr>
<tr>
<td>i.d.</td>
<td>internal diameter</td>
<td>MOT</td>
<td>multiple occlusion</td>
</tr>
<tr>
<td>II</td>
<td>initial inspiratory</td>
<td>ms</td>
<td>millisecond</td>
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<td>kg</td>
<td>kilogram</td>
<td>MUF</td>
<td>modified ultrafiltration</td>
</tr>
<tr>
<td>kPa</td>
<td>kilopascal</td>
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</tr>
<tr>
<td>L</td>
<td>length</td>
<td>P</td>
<td>pressure</td>
</tr>
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<td>L</td>
<td>litre</td>
<td>Pa</td>
<td>pascal</td>
</tr>
<tr>
<td>L</td>
<td>lung</td>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>LRI</td>
<td>lower respiratory illness</td>
<td>PEF</td>
<td>peak expiratory flow</td>
</tr>
<tr>
<td>M</td>
<td>male</td>
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<td>PEFV</td>
<td>partial expiratory flow-volume curve</td>
<td>rs</td>
<td>respiratory system</td>
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<tr>
<td>pl</td>
<td>pleural</td>
<td>RTC</td>
<td>rapid thoraco-abdominal compression technique</td>
</tr>
<tr>
<td>pleth</td>
<td>plethysmographic</td>
<td>RV</td>
<td>residual volume</td>
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<td>postnatal age</td>
<td>s</td>
<td>second</td>
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<td>pneumotachograph</td>
<td>SBT</td>
<td>single breath technique</td>
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<tr>
<td>PTEF</td>
<td>peak tidal expiratory flow</td>
<td>SCM</td>
<td>single compartment model</td>
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<td>peak tidal inspiratory flow</td>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>QDC</td>
<td>qualitative diagnostic calibration</td>
<td>sGsw</td>
<td>specific airway conductance (Gsw/FRC)</td>
</tr>
<tr>
<td>QS</td>
<td>quiet sleep</td>
<td>SIMV</td>
<td>synchronised intermittent mandatory ventilation</td>
</tr>
<tr>
<td>R</td>
<td>flow resistance</td>
<td>T</td>
<td>tidal</td>
</tr>
<tr>
<td>R</td>
<td>respiratory</td>
<td>t</td>
<td>time</td>
</tr>
<tr>
<td>r²</td>
<td>coefficient of determination</td>
<td>tₑ</td>
<td>expiratory time</td>
</tr>
<tr>
<td>RASP</td>
<td>Respiratory Analysis Program</td>
<td>ti</td>
<td>inspiratory time</td>
</tr>
<tr>
<td>RC</td>
<td>ribcage</td>
<td>t_{PTEF}</td>
<td>time to peak tidal expiratory flow</td>
</tr>
<tr>
<td>RIP</td>
<td>respiratory inductance plethysmograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abbreviation</td>
<td>description</td>
<td>abbreviation</td>
<td>description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>$t_{tot}$</td>
<td>duration total</td>
<td>$V$</td>
<td>gas flow</td>
</tr>
<tr>
<td></td>
<td>respiratory cycle</td>
<td>$V_{max}$</td>
<td>maximal expiratory flow</td>
</tr>
<tr>
<td>tot</td>
<td>total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tp</td>
<td>transpulmonary</td>
<td>$V_{max,FRC}$</td>
<td>maximal expiratory flow at FRC</td>
</tr>
<tr>
<td>TAA</td>
<td>thoraco-abdominal asynchrony</td>
<td>$\Delta$</td>
<td>delta; change in variable</td>
</tr>
<tr>
<td>URTI</td>
<td>upper respiratory tract infection</td>
<td>$\mu g$</td>
<td>microgram</td>
</tr>
<tr>
<td>$V$</td>
<td>gas volume</td>
<td>$^\circ$</td>
<td>degree</td>
</tr>
<tr>
<td>$V_T$</td>
<td>tidal volume</td>
<td>$^\circ C$</td>
<td>degree Celsius</td>
</tr>
</tbody>
</table>

**Conversion factors**

- **Pressure**
  - $1 \text{ cmH}_2\text{O} = 0.098 \text{ kPa}$
  - $1 \text{ mmHg} = 0.133 \text{ kPa}$

- **Compliance**
  - $1 \text{ mL}\cdot\text{cmH}_2\text{O}^{-1} = 10.2 \text{ mL}\cdot\text{kPa}^{-1}$

- **Resistance**
  - $1 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s} = 0.098 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$
Aknowledgements

The work presented in this thesis was completed with the help and cooperation of many parents, colleagues and fellow workers. In particular, Dr K Costeloe, Dr C Dezateux, Ms I Dundas, Dr M Fletcher, Dr M Gappa, Ms A Hoo, Dr P Mannix, Ms L Pilgrim, the staff of the Special Care Baby Unit of the Homerton Hospital and the theatre, ward, outpatient and intensive care staff of the Great Ormond Street Hospital for Children.

I thank my supervisors, Dr J Stocks and Professor DJ Hatch and acknowledge the financial support of Portex, Hythe, England.

Declaration

I was involved in all the research studies presented in this thesis, some of which were undertaken jointly with others.

I was responsible for the study design and the majority of the measurements as well as the data analysis for the studies described in Sections 4.3, 4.5, 5.1, 5.2 and 5.3. Isobel Dundas undertook the plethysmographic measurements reported in section 4.5 and the study in Section 5.4 was undertaken jointly with Dr Gappa.

For the studies presented in Sections 4.1, 4.2 and 4.4 I was involved in data collection and analysis. Most of the subjects had been recruited to ongoing epidemiological research projects being undertaken by others in the department.
1. Introduction and aims

Respiratory problems are a common cause of morbidity in the first few years of life. Up to 40% of infants wheeze during the first year of life, some of whom will go on to develop childhood asthma, the prevalence of which is increasing. Respiratory disease is especially important in very preterm infants who are at particular risk of developing chronic lung disease. Knowledge of the growth and development of the respiratory system is essential to the understanding of the effects of disease and how to prevent and minimise damage to the lungs. In addition, objective assessments of respiratory function may contribute to the diagnosis and management of disease.

Respiratory function testing, using spirometry, for clinical, epidemiological and research purposes in adults and older children has been established for over 50 years. Measurements in infants have lagged behind largely related to the fact that infants are unable to cooperate with voluntary respiratory manoeuvres and need to be measured during sleep. This frequently necessitates sedation which adds to the duration of testing, may preclude the sickest infants, can create parental anxiety and raises ethical issues when measurements are required primarily for research.

Despite the difficulties, the last 15 years have seen increasing interest in respiratory function testing in infants. Initial tests were modified from those used in adults, for example dynamic mechanics and measures of lung volume. Subsequently simpler and less invasive tests were developed specifically for infants, including passive respiratory mechanics measurements and the rapid thoraco-abdominal compression technique to obtain forced expiratory flow volume curves. Still more recently there has been interest in the evaluation of tidal breathing parameters for the assessment of airway function.

At the inception of this thesis in 1991, infant lung function testing had become established for both population based (epidemiological) and clinical research studies. Lung function testing was also being utilised in the management of individual patients although this application was more controversial, being largely based on clinical experience rather than research evidence. The volume of epidemiological and clinical research was increasing rapidly as was the clinical use of lung function...
testing. This was partly as a result of the recently developed simpler methods of testing lung function and technological advances including the introduction of commercially available automated equipment. Neither the simpler methods nor the technological developments had been thoroughly evaluated.

The main aim of this thesis was to evaluate critically recent advances in infant respiratory function testing in both spontaneously breathing infants and infants receiving respiratory support. A series of studies is presented each with its own introduction, methodology and discussion. In the final section the main findings of these studies are summarised and the implications of both this work, and published research into infant respiratory function testing by others, discussed. Table 1.1 provides an outline of the main contents of each section.
Table 1.1: Thesis plan

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<th>Section</th>
<th>Main contents</th>
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<td>The history of infant respiratory function testing</td>
</tr>
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<td>2.1</td>
<td>a review of the development of infant respiratory function testing up to the inception of this thesis in 1991</td>
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<td>2.2</td>
<td>a summary of current applications of infant respiratory function tests</td>
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<td>2.3</td>
<td>a summary of the obstacles to the use of infant respiratory function tests at the inception of this thesis</td>
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<td>3.</td>
<td>Methods</td>
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<td></td>
<td>a theoretical background to infant respiratory function testing</td>
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<td>a description of the apparatus and methods used in the thesis</td>
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<tr>
<td>4.1-4.4</td>
<td>studies evaluating simpler methods of assessing airway function ($t_{\text{RTF}}$ and $t_{\text{E}}$ and passive mechanics)</td>
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<td>4.5</td>
<td>a longitudinal study of respiratory function in infants with oesophageal atresia</td>
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<td>5.</td>
<td>Respiratory function testing in infants receiving respiratory support</td>
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<tr>
<td>5.1</td>
<td>a pilot study of respiratory function in infants undergoing cardiac surgery discussing difficulties of current methods</td>
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<tr>
<td>5.2-5.3</td>
<td>assessments of automated respiratory function monitors, the development of standards for such equipment</td>
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<td>5.4-5.5</td>
<td>assessments of a catheter tipped micro-transducer for monitoring oesophageal pressure and dynamic mechanics</td>
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<td>6.</td>
<td>Discussion</td>
</tr>
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<td></td>
<td>The main findings are summarised and discussed with the work of others to address:</td>
</tr>
<tr>
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<td>the limitations of simpler tests of respiratory function</td>
</tr>
<tr>
<td>6.3</td>
<td>the contribution and limitations of technological advances</td>
</tr>
<tr>
<td>6.4</td>
<td>appropriate respiratory function tests for research and clinical purposes</td>
</tr>
<tr>
<td>6.5</td>
<td>future directions for research</td>
</tr>
</tbody>
</table>
2. The history of infant respiratory function testing

This section will provide;

- a review of the development of infant respiratory function tests up to the inception of this thesis in 1991
- a summary of the current research and clinical applications of infant respiratory function tests
- a summary of the obstacles to the use of infant respiratory function tests at inception of this thesis

2.1 The development of infant respiratory function testing

2.1.1 Early measurements

Attempts at measuring adult respiratory function date from the 1700s when Humphrey Davy made the first lung volume measurements. The water spirometer was introduced for use in adults in 1846. Measurements in infants lagged behind; it was not until the 1890s that Eckerlein and Dohrn measured tidal ventilation in infants using a small spirometer attached to a face mask. The equipment used had excessive dead space and reasonable accuracy was not obtained until the introduction of the head-out plethysmograph by Murphy and Thorpe in 1931. This permitted determination of tidal ventilation without any apparatus dead space. The apparatus was refined by Cross in 1949 who introduced a better neck seal and reported tidal breathing parameters for term infants. The early plethysmographs incorporated water spirometers but a transducer system was introduced in 1950.

2.1.2 Dynamic mechanics measurements

The measurement of dynamic mechanics became established in the 1950s. The concept of mechanical analysis of the respiratory system on which the measurements are based dates from a series of studies published by Rohrer in 1915 in which he established the basic relationship between pleural pressure, lung elastic recoil pressure and alveolar pressure. Although Neergaard and Wirz applied these principles to a series of experiments in the 1920s it was not until the 1950s, following the introduction of electrical recording apparatus and the acceptance of oesophageal pressure as an indirect measure of pleural pressure, that significant
numbers of measurements appeared. The first oesophageal balloon was described in 1952\textsuperscript{13} and the following year Mead and Whittenberger published a description of dynamic lung mechanics measurements in adults.\textsuperscript{14}

The first reports of dynamic mechanics measurements in healthy newborns was published by McIlroy and Tomlinson in 1955.\textsuperscript{15} In 1960 Karlberg et al published their methodology for the measurement of dynamic respiratory mechanics in the newborn and highlighted the usefulness of pressure-volume plots of individual breaths to allow visual evaluation of respiratory mechanics.\textsuperscript{16} In these early studies, tidal volume and flow were measured using the head out plethysmograph as, although the pneumotachograph was introduced by Fleisch in 1925, the first low dead space model for use in infants was not introduced until 1960.\textsuperscript{17}

During the 1950s and early 1960s a series of articles described improved techniques, including the development of the occlusion test and the appropriate characteristics for oesophageal balloons for measurements in adults.\textsuperscript{18-21} The occlusion test is used to demonstrate that changes in oesophageal pressure accurately reflect those of pleural pressure. The test requires the subject to make respiratory efforts against an occluded airway and is therefore not applicable to paralysed subjects. Improvements in the use of oesophageal balloons for measurements in infants were described by Beardsmore et al in 1980.\textsuperscript{22} In the 1970s and 1980s a number of studies in both animals\textsuperscript{23} and sick neonates\textsuperscript{24-26} were published that suggested oesophageal pressure may not always reflect mean pleural pressure in the presence of chest wall distortion. These findings cast doubt on the method for assessing sick infants and on previously performed studies using this technique in which the occlusion test had not been performed.

Although oesophageal balloons have been the most popular method of measuring oesophageal pressure, liquid filled catheters have been described for use in adults\textsuperscript{27} and in infants.\textsuperscript{28} Catheter tipped transducers consisting of miniaturised transducers mounted on flexible catheters have also been used in both adults\textsuperscript{29} and infants.\textsuperscript{30} Their use has been limited in part due to claims that they overestimate pleural pressure.\textsuperscript{30}

The Mead and Whittenberger technique for analysing dynamic mechanics, first established in 1953,\textsuperscript{14} remains a commonly used method. However the method has
limitations especially when analysing data from mechanically ventilated subjects in whom total respiratory mechanics may be measured without oesophageal pressure monitoring if the infant is making no respiratory effort. Advances in computer technology led to more complex methods of analysis being developed during the 1970s and 1980s, based on least squares regression\(^{31,33}\) and multiple linear regression (MLR).\(^{34}\) In contrast to other methods, MLR allows data to be analysed in terms of more complex models of the respiratory system than a linear single compartment model.

Another method of assessing dynamic respiratory mechanics involves imposing oscillatory changes in flow at the airway opening and calculating respiratory impedance which reflects both resistive and elastic properties (forced oscillation technique).\(^{35}\) Although the technique was first introduced by DuBois et al in 1956\(^{36}\) it has been used relatively little. In the late 1980s the method was reappraised\(^{35}\) and Sly et al suggested it may prove useful in ventilated infants.\(^{37}\)

### 2.1.3 Lung volume measurements and plethysmography

Soon after the measurement of dynamic mechanics became established, methods of measuring functional residual capacity (FRC) that could be adapted for use in infants were developed. Early measurements of lung volumes involved gas dilution techniques. The first measurements in infants were published in the late 1950s\(^{38,39}\) and used helium dilution which had first been described for use in adults by Willmon and Behnke in 1948.\(^{40}\) The early helium dilution methods were only suitable for spontaneously breathing infants. Measurements in sick infants were not possible until 1970 when a system incorporating a rebreathing bag was introduced by Krauss and Auld.\(^{41}\)

Although the nitrogen washout technique was suggested by Darling et al in 1940,\(^{42}\) measurements in infants using nitrogen as a tracer gas lagged behind measurements using helium. The use of nitrogen as a tracer gas during air wash-in after oxygen breathing was first reported in infants in 1962\(^{43}\) however it was not until 1975 that Ronchetti et al first described nitrogen washout measurements.\(^{44}\) The method was simplified in the 1980s by the development of methods using open rather than closed
circuits. The method was adapted for use in ventilated infants by Sivan et al in 1990.

In the mid 1950s, at the same time as the helium dilution method was being developed for use in infants, whole body plethysmography was being developed for the measurement of FRC and airway resistance in adults by DuBois et al. This method was adapted for use in infants for the measurement of FRC in 1960 and for the measurement of airway resistance in 1961 by Polgar. With further modifications, including the addition of a heated rebreathing circuit in the 1970s, the whole body plethysmograph became established as a standard method for measuring FRC and airway resistance in infants.

2.1.4 Techniques developed primarily for use in infants
The relative complexity and invasiveness of whole body plethysmography and oesophageal manometry led to the development of tests specifically for infants; including passive respiratory mechanics and the rapid thoraco-abdominal compression technique.

2.1.4.1 Passive respiratory mechanics; multiple occlusion technique
Comroe et al in 1954 were the first to publish measurements of respiratory mechanics using a passive expiration in anaesthetised cats and adults. Originally, passive respiratory mechanics measurements were limited to paralysed or highly trained subjects because of the need for muscle relaxation. In 1976 Glinsky became the first to make use of the apnoeic pause, with respiratory muscle relaxation, induced in infants by the Hering-Breuer Inflation reflex, to study passive mechanics in unsedated infants. He developed the multiple occlusion technique (MOT) in which a series of airway occlusions is made during inspiration allowing a pressure-volume plot for the respiratory system to be constructed; the slope representing static compliance. In 1982 Mortola modified the technique by using expiratory rather than inspiratory occlusions, which improved both the likelihood of successful measurement and the reproducibility of measurements. More recently the multiple occlusion method has been adapted to obtain the static pressure-volume relationship by making multiple occlusions during a single expiration – the multiple interrupter technique.
2.1.4.2 Passive respiratory mechanics; single breath technique
In 1982 Mortola described the measurement of the respiratory time constant and calculated respiratory resistance using this time constant and compliance, as assessed from the MOT. In the same year Zin developed the single breath technique (SBT) in anaesthetised, but unparalysed cats, in which respiratory system compliance and resistance are measured from single breaths. A similar approach was described in spontaneously breathing and mechanically ventilated neonates by Le Souëf et al in 1984 and by Thomson et al in 1985.

2.1.4.3 Passive respiratory mechanics; interrupter technique
The interrupter technique, which involves very rapid flow interruption and sophisticated analysis of the pressure and volume changes during a relaxed occlusion was originally suggested by Neergaard and Wirz in the 1920s. The method was used in the 1950s but then essentially discarded as it was unclear what the technique measured. In the 1980s Bates et al reappraised the technique demonstrating that airway resistance and the compliance and viscoelastic properties of the respiratory system were being assessed. In 1988 Sly et al suggested the interrupter technique may prove useful in ventilated infants.

2.1.4.4 Passive respiratory mechanics; weighted spirometry
Although weighted spirometry for the measurement of respiratory compliance was first described in adults and older children in 1965, it has more recently been applied in infants.

2.1.4.5 The rapid thoraco-abdominal compression technique
Adler in 1978 first described a means of obtaining partial expiratory flow volume curves in normal sedated infants by means of rapid thoraco-abdominal compression. This technique was further developed in the 1980s by the introduction of an inflatable jacket and, due to its relative simplicity, has become one of the most extensively used techniques for assessing airway function in infants. In adults, the use of the full lung volume range for assessing voluntary forced expirations has been found to provide more useful information than the use of the tidal volume range. Although full maximal expiratory flow volume curves had been obtained in intubated infants by
applying negative pressure after passive inflation in the 1970s\textsuperscript{73} there had been no reports of raised lung volume assessments in spontaneously breathing infants at the inception of this thesis.

2.1.5 Tidal breathing parameters
Abnormalities of tidal expiratory flow pattern were noted in adults with respiratory diseases in the 1940s\textsuperscript{74-76} and were first reported in children with asthma and cystic fibrosis in 1949 by Kaye et al\textsuperscript{77} who suggested tidal flow recordings could be clinically useful. However it was not until 1981 that Morris and Lane proposed the detailed analysis of tidal expiratory flow pattern as a quantitative method for assessing lower airway function based on studies in adults.\textsuperscript{78} Subsequently, reports of quantitative analyses of tidal expiratory flow patterns in infants with bronchopulmonary dysplasia appeared which concluded that such infants reach tidal peak expiratory flow more rapidly than age matched normals.\textsuperscript{79,80}

The need for very simple measures of respiratory function in infants that can be applied in large epidemiological studies, preferably without the need for sedation, has led to a recent renewed interest in the analysis of tidal flow patterns.

2.1.6 Body surface measurements
All the methods described so far require accurate measurement of airflow and volume changes, which are most commonly measured with a pneumotachograph. However pneumotachographs may themselves affect ventilation,\textsuperscript{81,82} require considerable technical expertise, and necessitate the use of a tight fitting face mask. Consequently there have been numerous efforts to develop less invasive methods of measuring tidal volume and respiratory timing. Methods that have been assessed in infants include impedance pneumography, magnetometers, strain gauges and respiratory inductance plethysmography (RIP). The most recently developed, RIP, which was described in 1977\textsuperscript{83} and assessed for use in infants in 1981,\textsuperscript{84} has been shown to be the most satisfactory for quantitative assessments.\textsuperscript{85,86} Various methods of calibration have been described\textsuperscript{87,88} including automated qualitative self calibration during tidal breathing (QDC).\textsuperscript{89} In addition surface measurements allow quantitative assessment
of thoraco-abdominal asynchrony which has been suggested as a method of assessing airway function.\textsuperscript{90,91}

2.2 Applications of infant respiratory function testing

At the inception of this thesis the main applications of infant respiratory function testing were in research, both clinical and population based. Table 2.1 gives a classification of research applications. The other more controversial area in which infant respiratory function testing was being used was in the clinical management of individual infants. Proposed clinical applications are also given in Table 2.1. The clinical applications were not clearly defined and were based largely on individual clinical experience rather than research evidence. The increasing availability of automated measuring devices was leading to the increased use of infant respiratory function testing especially in ventilated neonates.

2.3 Obstacles to the use of infant respiratory function tests

The main obstacle to high quality research using respiratory function measurements as outcome parameters was the lack of ideal methods. The available methods suffered from one or more major disadvantage;

- they were highly complex, and therefore expensive and limited to specialist laboratories
- there was a lack of suitable reference values and limited knowledge about intra and inter subject variability
- they made fundamental assumptions that may not be met particularly in sick infants (e.g. that the respiratory system can be described by a single time constant when using the single breath technique)
- they required the infant to be asleep therefore necessitating sedation in most circumstances
- the relationship between the measured variable and respiratory mechanics was poorly understood (e.g. $I_{PEE}$, $I_{E}$)

As a result many of the studies that had been published could be criticised because of the use of unsuitable techniques or poor interpretation. Many studies involved inadequate numbers of subjects probably in part due to the time consuming nature of the measurements. Problems were greatest in the intensive care setting as many
studies failed to consider the particular difficulties of measuring intubated and ventilated infants.

In the late 1980s several clinicians suggested that monitoring of respiratory mechanics should be clinically useful especially during assisted ventilation. At the time there was minimal evidence to support this view with only one preliminary report of a study showing an effect on morbidity when ventilator settings were altered according to regular pulmonary function testing in infants. A possible explanation for the lack of evidence was "the absence of a simple non-invasive and precise technique for the rapid quantitative determination of respiratory system mechanics in ventilated patients" (Gillard et al,1990).
Table 2.1: Applications of infant respiratory function tests

<table>
<thead>
<tr>
<th>Research applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  <em>Population based studies</em></td>
</tr>
<tr>
<td>i) to define normal lung growth and development</td>
</tr>
<tr>
<td>ii) to evaluate risk factors for subsequent respiratory disease</td>
</tr>
<tr>
<td>II  <em>Clinical research studies</em></td>
</tr>
<tr>
<td>i) to define and quantitate pathophysiological processes</td>
</tr>
<tr>
<td>ii) to evaluate treatments including the short and long term effects of interventions and comparative studies</td>
</tr>
<tr>
<td>- drugs e.g. bronchodilators and surfactant</td>
</tr>
<tr>
<td>- modes of respiratory support including mechanical ventilation and extra-corporeal membrane oxygenation</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential clinical applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) to assist in diagnosis</td>
</tr>
<tr>
<td>ii) to assess disease severity and predict outcome</td>
</tr>
<tr>
<td>iii) to monitor disease progression</td>
</tr>
<tr>
<td>iv) to evaluate and optimise therapies in individual infants</td>
</tr>
<tr>
<td>- drugs e.g. bronchodilators and surfactant</td>
</tr>
<tr>
<td>- modes of respiratory support especially mechanical ventilation</td>
</tr>
</tbody>
</table>
3. Equipment and methods

This section provides a theoretical background to infant respiratory function testing and a description of the equipment and the methods of measuring respiratory function used in this thesis. New respiratory function testing equipment assessed as part of the thesis and adaptations required for specific protocols are described in the relevant sections.

3.1 Pressure, airflow and volume measurement

The majority of infant respiratory function tests involve the measurement of airflow and volume changes at the airway opening, and the measurement of pressure changes.

3.1.1 The theory of pressure, airflow and volume measurements

3.1.1.1 Pressure transducers

Most pressure transducers consist of a chamber containing a diaphragm which is coupled to a sensing element. Movement of the diaphragm alters the electrical conductivity of the sensing element altering the electrical signal produced. The chamber of the pressure transducer is usually connected to the pressure source by tubing. Changes in pressure are transmitted to the transducer by displacement of small volumes of gas (or liquid) in the tubing, with the resulting change in chamber volume causing displacement of the diaphragm. Many transducers have connection ports on both sides of the diaphragm (differential pressure transducers) and hence their output is determined by the pressure difference across the diaphragm. Differential pressure transducers are used with most flow measuring devices as well as being used to measure pressures (e.g. at the airway opening) relative to atmospheric pressure.

The dynamic performance of pressure transducers depends on:
- damping
- linear range
- coefficient of displacement
- frequency response

3.1.1.1 Damping

Following a step change in input, a transducer responds with an output. The accuracy of the response depends on the physical characteristics of the transducer and its
connecting tubing. In the absence of any resistance in the tubing, the transducer output for a step change in input will overshoot and then oscillate around the new mean value. This is described as underdamped. As the amount of resistance in the system increases, the output for a step change in input will approach the new mean value without overshoot and without oscillation. This is described as critically damped. Further increases in resistance will result in overdamping with a delay in the output signal reaching the new steady state value. See Figure 3.1.

**Figure 3.1: Critical damping of transducer signal**

![Diagram showing critical damping of transducer signal](image)

- **a)**: undamped, **b)**: underdamped, **c)**: critically damped, **d)**: overdamped.

### 3.1.1.1.2 Linear range

The linear range of a transducer describes the range of amplitudes over which the output from the transducer is able to accurately reproduce the input. Failure to keep within the linear range of a transducer results in inaccurate measurements.
3.1.1.1.3 Coefficient of displacement
The coefficient of displacement is defined as the change in volume of the transducer per unit change in pressure ($\Delta V/\Delta P$). The coefficient of displacement should be as small as possible, requiring minimal physical displacement of gas or liquid in the connecting tubing and transducer. This is particularly important when measuring oesophageal pressure as when the coefficient is large, relative to the inherent pressure-volume characteristics of the oesophagus, pressure will be lost within the oesophagus itself in order to displace the transducer diaphragm. This will result in an underestimate of pleural pressure.\textsuperscript{96}

3.1.1.1.4 Frequency response
Frequency response defines the ability of a device to reflect changing signals accurately. Frequency response has two components;
- magnitude, usually expressed as attenuation, the ratio between the output and input signals
- phase, the temporal relationship between the input and output signals, expressed either in degrees or as a time lag

The frequency response of equipment depends on;
- dimensions
- compliance
- medium being measured

In general, the larger the diameter and shorter the length of the equipment, including connecting tubing, the better the frequency response. The less compressible the medium and the lower its inertia the better the frequency response. However, other factors including coefficient of displacement, damping and practicality also have to be considered.

A greater frequency response is required for infant measurements than measurements in older children and adults because of their higher respiratory rates. The need to minimise dead space makes achieving a good frequency response more difficult. The minimum requirement for frequency response for infant respiratory function testing has not been clearly defined.\textsuperscript{97} A good frequency response to 10 Hz has been
suggested as adequate for spontaneously breathing infants, with values of between 20 and 100 Hz being suggested for ventilated infants.

### 3.1.1.2 Flow and volume measurement

The measurement of flow or volume changes is essential to most measurements of respiratory function. As flow is the rate of change of volume, it is usual to measure one and derive the other. In this thesis, flow has been measured and digitally integrated to give volume, the only exception being when respiratory inductance plethysmography has been used (see Section 3.5.2). Only flow measuring devices will be considered further.

For the measurement of air flow at the airway opening of infants, a flow measuring device must have the following characteristics:

- predictable steady state response
- adequate working range
- adequate frequency response
- small or predictable dependence on gas temperature, humidity and composition
- low dead space
- low resistance to airflow

In addition ideally it should be easy to use.

#### 3.1.1.2.1 Steady state response

The steady state response is the relationship between constant applied flows and the output signal of the device. A linear relationship between the flow and the output of the flow meter simplifies calibration and calculation of tidal volumes and mechanics. However, this has become far less important with advances in computer technology that permit most non-linearities to be removed digitally, provided adequate calibration facilities exist.

#### 3.1.1.2.2 Working range

The working range of a flow meter describes the range of steady state flows that the instrument can measure accurately. The working range must encompass the maximum flows achieved by the infant. This will depend on the size of the infant, whether the infant is breathing spontaneously, is mechanically ventilated or has
increased flows related to airway occlusions or forced expiratory manoeuvres. The maximum flow capability is usually limited by nonlinearities at high flows. Even if such nonlinearities are digitally corrected the resistance of the flow meter may become unacceptable. In general, the greater the maximum flow that can be measured the less sensitive the flow meter is at low flows. Sensitivity at low flows is usually limited by noise in the measurement system and limited resolution of the signal amplification and display system. Poor performance at low flows leads to inaccuracies in integrated values i.e. volume measurements.

3.1.1.2.3 Frequency response
Frequency response refers to the ability of a measuring device to reflect rapidly changing signals accurately as discussed previously in Section 3.1.1.1.4. For the most commonly used flow measuring devices (linear resistive pneumotachographs) frequency response is determined largely by the transducer and connecting tubing rather than the actual pneumotachograph.

3.1.1.2.4 Response to temperature and gas composition
Expired gas differs from inspired gas in terms of temperature, humidity and the partial pressures of oxygen and carbon dioxide. Measurements are often made with infants breathing warmed, humidified and oxygen enriched air. If measurements are made during anaesthesia nitrous oxide may be used. Different gases will have different densities and viscosities. An ideal flow meter would have a response that is independent of the physical characteristics of the gases measured.

3.1.1.2.5 Dead space and resistance
An ideal flow meter has both a low dead space and a low resistance across the working range of flows. In general the smaller the device the higher the resistance and the less the working range. Smaller infants require lower dead space devices but can tolerate higher added resistance as their respiratory resistance is higher.

3.1.1.3 Types of flow measuring device
Several devices have been used to measure flow, the most popular being linear resistance pneumotachographs (PNTs). The linear resistance consists of either multiple parallel capillary tubes (Fleisch type) or a fine wire mesh screen. In both
types laminar flow is generated and a pressure drop develops that is dependent on the flow and the viscosity of the gas. The pressure gradient is measured using a differential pressure transducer and amplifier. The frequency response of the PNT-pressure transducer system is greatly influenced by the connections between the PNT and transducer. This is considered further in Section 3.1.1.4.1. Commercially available Fleisch and screen PNTs come in a range of sizes to suit preterm infants to adults. The minimum measured flow depends on the differential pressure transducer and amplifier used.

Many other types of flow meter have been described including;

- ultrasonic flow meters (see Section 6.3.2)
- hot wire anemometers (see Section 6.3.2)
- nonlinear differential pressure based flow meters, e.g. variable orifice (see Section 5.3) and pitot tubes (see Section 5.2)

3.1.1.4 Flow measuring devices; practical considerations

3.1.1.4.1 Influence of connectors

Flow meters are sensitive to the distribution of flow which is influenced by the geometry of the connectors and tubing (including tracheal tubes) on either side of the flow meter. Both calibration and frequency response may be altered. Apparatus should therefore be both calibrated and assessed as used for measurements (see Section 5.3: The assessment of neonatal pulmonary monitors).

3.1.1.4.2 Gas composition, temperature and secretions

Most linear resistive PNTs are used with a heating shell to prevent condensation altering the resistance. Heating also prevents changes in gas viscosity between inspired and expired gas that otherwise occur due to temperature differences. Changes in gas composition e.g. the use of added oxygen or of anaesthetic gases will also alter viscosity. It is therefore important that PNTs are calibrated using an appropriate gas mixture. Secretions deposited within the PNT during prolonged measurements can affect calibration. This is a particular problem in intubated infants but can be minimised by the use of suction prior to measurements. Calibration checks at the end of a study are necessary to identify the problem.
3.1.1.4.3 Pressurisation of PNTs during IPPV
When a PNT is used within a ventilator circuit during intermittent positive pressure ventilation (IPPV) it is subjected to pressure swings as gas is driven into the patient’s lungs. The pressure changes are usually large relative to the changes due to flow across the PNT. There is no problem provided the airway pressure reaches both sides of the diaphragm of the differential pressure transducer simultaneously so that the differential pressure remains zero. However, any asymmetry in the construction of the transducer or the connecting tubing will result in a differential pressure giving an erroneous flow measurement.

3.1.1.5 Combining flow and pressure measuring equipment
When combining measuring devices to measure respiratory function, the frequency response of each transducer must be matched i.e. the equipment must not introduce an artefactual phase difference between pressure and flow changes. Combining equipment may degrade the frequency response of the components which should therefore be assessed for the fully assembled equipment. Care is necessary to ensure the airway opening pressure port is not placed in too narrow a part of the circuit or the pressure may be underestimated due to the Bernoulli effect. When devices are combined it is important to consider the total dead space and resistance.

3.1.1.6 Signal processing
The output of most transducers is in the order of microvolts or millivolts. In order to display and process the signals they must be amplified. Amplifiers usually have adjustable sensitivity or gain and often incorporate filters. Filtering is the process whereby the relative amplitudes and phases of signals are changed in a systematic and frequency dependent way. The most commonly used filters during the measurement of respiratory mechanics are low-pass filters which attenuate or remove high frequency signals. Signals that are to be processed by computer must be low-passed filtered to prevent aliasing. Aliasing is the distortion that results when high frequency signals are sampled at lower frequency. Filters are also used to eliminate unwanted signals (noise). As filtering usually produces some phase change, it is important to filter all simultaneously collected signals in an identical manner.
Most measurements of respiratory mechanics are now made using computers. The voltage signal generated by the amplifiers must be digitised using an analog to digital converter. The analog signal is continuous but the computer stores a digital representation at defined intervals. The sampling frequency must be adequate to reproduce the analog signal faithfully. Respiratory signals can be described in terms of a fundamental frequency and a series of harmonics. The number of harmonics that need to be included depends on the complexity of the waveforms. The sampling frequency needs to be at least twice the highest harmonic frequency of interest. Recommended sampling frequencies and the measurement errors introduced by using lower sampling rates have been published. It is usual for the computer to integrate the flow signal digitally to generate a volume signal. Digital filtering to correct for zero offset is often performed before further data analysis.

3.1.2 Equipment for pressure, flow and volume measurements
This section provides details of the measuring equipment used for this thesis.

3.1.2.1 Pressure transducers
Unless otherwise stated, pressures were measured with Validyne (Northridge, CA) MP45 differential pressure transducers or Furness (Sussex, England) FC044 differential pressure transducers used with Validyne or Furness signal conditioning modules respectively. All simultaneously collected signals were collected with the same make of transducer. The low pass analog filters were set at 10 Hz unless otherwise stated. Transducers with linear ranges of ±0.2 kPa and ±5 kPa were used with PNTs and to measure pressure at the airway opening respectively. Low compliance, 3 mm internal diameter, translucent vinyl tubing (Portex, Hythe, England) was used to connect the transducers to the pressure ports on the PNTs or at the airway opening. The minimum practical lengths of tubing were used and identical lengths used with all simultaneously used transducers.

3.1.2.2 Pneumotachographs
Unless otherwise stated, flows were measured using Fleisch (Lausanne, Switzerland) size 0 or 1 PNTs or Hans Rudolph (Kansas City, MO) 0-10 or 0-35 L·min⁻¹ screen PNTs. The choice depended on the infant's maximum flows and the ease with which
the different PNTs connected with other components of the measuring apparatus. All
PNTs were heated with shell heaters. Where connectors were required they were
constructed to avoid both excessive dead space and sudden changes in geometry that
may have resulted in turbulence. The PNTs were all used within their linear ranges.
The physical characteristics of the PNTs are given in Table 3.1.

Table 3.1: Characteristics of pneumotachographs

<table>
<thead>
<tr>
<th>Pneumotachograph</th>
<th>Dead space</th>
<th>Resistance†</th>
<th>Linear range‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleisch 0</td>
<td>2.5</td>
<td>0.43</td>
<td>±15</td>
</tr>
<tr>
<td>Fleisch 1</td>
<td>10</td>
<td>0.10</td>
<td>±27</td>
</tr>
<tr>
<td>Fleisch 0 + cable release shutter</td>
<td>7.6</td>
<td>0.48</td>
<td>±15</td>
</tr>
<tr>
<td>Fleisch 1 + cable release shutter</td>
<td>15</td>
<td>0.11</td>
<td>±27</td>
</tr>
<tr>
<td>Fleisch 0 + plethysmograph shutter</td>
<td>7.6</td>
<td>0.78</td>
<td>±15</td>
</tr>
<tr>
<td>Fleisch 1 + plethysmograph shutter</td>
<td>26</td>
<td>0.48</td>
<td>±27</td>
</tr>
<tr>
<td>Hans Rudolph 0-10 L·min⁻¹</td>
<td>1.3</td>
<td>1.11</td>
<td>±10</td>
</tr>
<tr>
<td>Hans Rudolph 0-35 L·min⁻¹</td>
<td>6.8</td>
<td>0.27</td>
<td>±35</td>
</tr>
</tbody>
</table>

†measured at 100 mL·s⁻¹; ‡accuracy within 3%.

3.1.2.3 Data processing

All signals were processed using IBM compatible 386 or 486 personal computers.
The analog outputs of the transducers were digitised using Analog Devices RTI 815
A-D converters. RASP (Respiratory Analysis Program, Physio Logic, Newbury,
England) software was used to process, display and record the data. Signals were
sampled at frequencies of between 50 and 200 Hz depending on the type of
measurements being made and respiratory frequency. The flow signal was integrated
digitally to yield volume. Data were collected in discrete epochs of 18-120 seconds
depending on the sampling frequency, the number of simultaneous signals recorded
and the version of the software used.
3.1.2.3.1 Calibration

Transducers for the measurement of pressure at the airway opening were calibrated by applying two known pressure signals: 0 and +20 cmH₂O (1.964 kPa) using a water manometer.

The flow signal was calibrated by applying two known flows: 0 and 100 or 150 mL·s⁻¹ (depending on the size of the infant to be measured) using calibrated rotameters (KDG 1100, Sussex, England). The RASP software also allowed flow to be calibrated by applying known volume signals using a calibrated syringe (Hans Rudolph). This method was usually preferred when gas mixtures other than air were used. Flow calibration was performed with the equipment assembled ready for use and using gases of the same composition as those used for the measurements.

All calibrations were checked prior to and after completion of each measurement session using known signals.

3.1.2.3.2 Data analysis

Data analysis was performed using RASP software. The program permits the operator to control data selection and apply acceptance criteria while automating the repetitive mathematical processes involved in data analysis. All algorithms for derived parameters had been validated in the respiratory laboratory at the Institute of Child Health.

3.1.3 The measurement of tidal breathing parameters

Tidal breathing parameters, in particular $t_{P_{PE}}$ (based on the measurement of airflow and volume are reported in Sections;

- 4.1: The reproducibility of $t_{P_{PE}}$ in infancy
- 4.2: The relationship between $t_{P_{PE}}$ and specific airway conductance
- 4.3: Uncalibrated respiratory inductance plethysmography for the measurement of tidal breathing parameters

Data for the analysis of tidal breathing parameters were collected during sleep (natural or sedated depending on the protocol) using an appropriately sized Fleisch or Hans Rudolph PNT (see Section 3.1.2.2) attached to a Rendell-Baker Soucek face mask (Rusch UK Ltd, High Wycombe). Where passive mechanics or
plethysmographic measurements were also required, tidal breathing measurements were made using the passive mechanics or plethysmography equipment (see Sections 3.2.4 and 3.3.2).

Analysis of tidal breathing data was performed using RASP software. Mean values are based on the analysis of a minimum of 2 epochs of data with between 20 and 50 breaths. Figure 3.2 shows a time based trace of tidal flow and volume labelled to illustrate how the commonly used tidal breathing parameters are defined.

**Figure 3.2: Tidal breathing parameters**

![Tidal breathing parameters](image)

Time based trace of tidal flow and volume. $t_i$: inspiratory time, $t_e$: expiratory time, PEF: peak expiratory flow and $t_{PEF}$: time to peak tidal expiratory flow.

### 3.2 Mechanics of breathing

The basic mechanics measurements are compliance and resistance. Compliance, a measure of elastic recoil, is defined as unit change in volume per unit change in pressure;

$$ C = \frac{\Delta V}{\Delta P} $$

where $C$ is compliance, $V$ is volume and $P$ is pressure.
Resistance is defined as unit change in pressure per unit flow;

\[ R = \frac{\Delta P}{\Delta V'} \]

where \( R \) is resistance, \( P \) is pressure and \( V' \) is flow.

The terms respiratory compliance (\( C_{\text{tn}} \)) and respiratory resistance (\( R_{\text{tn}} \)) describe the combined properties of the lung and chest wall, whereas the terms pulmonary or lung compliance (\( C_L \)) and resistance (\( R_L \)) are used to describe the properties of the respiratory system less the chest wall (i.e. lungs and airways). Airway resistance (\( R_{\text{aw}} \)) is the resistance of the airways alone. The reciprocal of compliance is referred to as elastance and the reciprocal of resistance is conductance.

Determination of compliance and resistance therefore requires simultaneous measurements of airflow, volume and applied pressure. The measurement methods can be classified as:

- dynamic measurements which are made during either spontaneous or mechanical breaths
- passive measurements which are made during periods in which the respiratory muscles are relaxed either by reflex inhibition or pharmacologically

Most measurement techniques assume that the behaviour of the respiratory system can be described by the equation of motion of a single compartment model with unique values for compliance and resistance;

\[ P = \left( \frac{1}{C} \cdot V \right) + (R \cdot V') + \left( I \cdot \frac{d^2V}{dt^2} \right) \]

where \( I \) is inertance and \( \frac{d^2V}{dt^2} \) is acceleration.

A further assumption of most methods is that inertance is negligible and the equation can be simplified to;

\[ P = \left( \frac{1}{C} \cdot V \right) + (R \cdot V') \]

### 3.2.1 The theory of dynamic mechanics measurements

In subjects who are mechanically ventilated and making no respiratory effort dynamic respiratory mechanics can be measured from simultaneous measurements of airflow,
volume and pressure at the airway opening. However, in spontaneously breathing infants it is necessary to measure transpulmonary pressure (i.e. the difference in pressure between the pleural space and the airway opening $P_{pl} - P_{ao}$) and calculate dynamic pulmonary mechanics. Changes in pleural pressure may be estimated from changes in oesophageal pressure ($P_{oes}$).

### 3.2.1.1 Oesophageal manometry

Three different methods of measuring oesophageal pressure in infants have been described;

- oesophageal balloon manometry
- fluidics manometry (liquid filled catheters)
- catheter tipped micromanometry

#### 3.2.1.1.1 Oesophageal balloon manometry

A catheter mounted balloon, containing a small but known volume of air, may be used to measure oesophageal pressure. The physical characteristics of the balloon are critically important as the balloon must have an acceptable "working range" i.e. a range over which changes in internal volume do not influence pressure within the balloon catheter system. The working range of each balloon should be tested before use. Oesophageal balloons do not reflect absolute oesophageal pressure accurately as they are influenced by balloon volume. However, as dynamic mechanics measurements only require changes in oesophageal pressure to be measured this is not a problem.

#### 3.2.1.1.2 Liquid-filled catheters

Liquid filled catheters may also be used to transmit oesophageal pressure to a transducer. A potential advantage is that they can be smaller than balloons and therefore less likely to produce oesophageal spasm. The absolute pressure will be influenced by changes in the relative levels of the transducer and catheter tip. However, as the measurement of pulmonary mechanics only requires the accurate recording of changes in oesophageal pressure, provided the infant and the transducer remain at the same level throughout the measurements this is not a problem. A potential disadvantage of liquid filled catheters is that they require frequent flushing.
to prevent air bubbles forming which damp the pressure response.

3.2.1.1.3 Catheter tip pressure transducers
Catheter tipped microtransducers, originally developed for invasive intra-vascular monitoring, have theoretical advantages. They require neither flushing nor careful adjustment of balloon volume. The assessment of a new catheter tipped transducer for the measurement of dynamic mechanics is described in Section 5.4.

3.2.1.1.4 Technical requirements
Whatever method of measuring oesophageal pressure is used, accurate measurement depends on adequate frequency response which is determined mainly by the connecting tubing of the system. Dynamic mechanics measurements are also critically dependent on the transducers used to measure $P_{oes}$, $P_{so}$ and flow being perfectly matched so that no phase lags exist between the signals.

It is important that the coefficient of displacement of the balloon or catheter with the tubing and transducer is low or pleural pressure will be underestimated (see Section 3.1.1.1.3).

3.2.1.1.5 Occlusion testing
It is necessary to confirm that the measured changes in oesophageal pressure accurately reflect pleural pressure. This requires an occlusion test, which is based on the assumption that, during periods of airway occlusion, there will be no flow of gas and pressures will equilibrate throughout the respiratory system. The occlusion test consists of comparing changes in oesophageal pressure ($P_{oes}$) and pressure at the airway opening ($P_{so}$) while the infant makes respiratory efforts against an obstruction at the airway opening. Although absolute pleural pressure ($P_{pl}$) differs from alveolar pressure by the static elastic recoil pressure of the lung, under conditions of no flow, $\Delta P_{pl}$ will be transmitted to the alveoli and can therefore be measured directly at the airway opening ($\Delta P_{so}$). Hence if $\Delta P_{oes}$ and $\Delta P_{so}$ are identical (i.e. $\Delta P_{oes} / \Delta P_{so} = 1$) $\Delta P_{oes}$ can be taken as a valid measure of $\Delta P_{pl}$ (see Figure 5.4.4).

Failure to achieve a satisfactory occlusion test with $\Delta P_{oes} / \Delta P_{so} = 1 \pm 0.05$ can arise in two situations;
• when $\Delta P_{oes}$ measured does not equal $\Delta P_{pl}$. This may be due to unsatisfactory balloon position, unsatisfactory balloon characteristics or increased oesophageal tone e.g. spasm or previous surgery.

• when $\Delta P_{oes}$ measured does not equal $\Delta P_{pl}$. This may be due to failure of equilibration of pressure during the airway occlusion which is most likely in rapidly breathing infants with long respiratory time constants (i.e. high compliance or elevated resistance). This may also occur in the presence of a leak at the airway opening.

An unsatisfactory occlusion test may occur in the presence of chest wall distortion although the mechanism is controversial.96

3.2.1.2 Calculation of dynamic mechanics

The calculation of dynamic compliance and resistance, from simultaneous measurements of airflow, volume and transpulmonary pressure has traditionally been based on the assumption that the lung (or respiratory system) can be represented by a single-compartment linear model in which transpulmonary pressure is the sum of the elastic and resistive pressures. Under these circumstances, a simplified general equation of motion can be applied to the lung as follows;

$$P_{tp} = E_l \cdot V + R_l \cdot V' + k \quad \text{equation 1}$$

where, at any point in time, $P_{tp}$ is the transpulmonary pressure, $E_l$ is the lung elastance, $V$ is the volume above elastic equilibrium volume, $R_l$ is lung resistance, $V'$ is flow and $k$ is a constant. The constant $k$ represents the sum of alveolar pressure at end expiration and any offset of the oesophageal pressure measuring device.

Several methods of calculating the mechanics values exist. Traditional methods developed to be performed manually have now largely been replaced by computerised methods. The Mead-Whittenberger method of analysis and the multiple linear regression approach will be described. Details of other methods can be found in published works.100

3.2.1.2.1 Mead-Whittenberger analysis

The Mead-Whittenberger technique14 was the most commonly used technique prior to the introduction of computerised data analysis. When the flow equals zero (i.e. at end
inspiration and end expiration), it is assumed that there are no flow resistive pressure losses and hence the generalised equation of motion (equation 1) can be simplified to;

$$\Delta P_p = \Delta P_{ei} = E_l \cdot \Delta V$$

or

$$E_l = \frac{\Delta P_p}{\Delta V}$$

where $\Delta V$ is the change in volume, $\Delta P_p$ is the change in transpulmonary pressure between end inspiration and end expiration and $\Delta P_{ei}$ is the pressure required to overcome the elastic recoil of the lung during a tidal breath (see Figure 3.3).

Since compliance is the reciprocal of elastance;

$$C_l = \frac{\Delta V}{\Delta P_p}$$

Similarly, at the same lung volumes during inspiration (e.g. mid-tidal volume) elastic recoil pressures are assumed to be equal but opposite, thereby cancelling out the viscoelastic pressure losses. Under these conditions the generalised equation of motion (equation 1) simplifies to;

$$\Delta P_p = \Delta P_{res} = R_l \cdot \Delta V'$$

or

$$R_l = \frac{\Delta P_p}{\Delta V'}$$

where $\Delta P_p$ and $\Delta V'$ are the changes in transpulmonary pressure and flow, respectively, between mid-inspiration and mid-expiration, and $\Delta P_{res}$ is the pressure required to overcome the resistive forces alone (see Figure 3.3).

This is the simplest technique to apply, however compliance and resistance are calculated using very few of the available data points. It is particularly unsuitable for measurements during mechanical ventilation when the pressure profile changes very abruptly at the points of zero flow (see Section 6.4.2.2).

### 3.2.1.2.2 Multiple linear regression analysis

Using computers, a least squares multiple regression (MLR) analysis technique can be used to solve the generalised equation of motion (equation 1). By measuring $\Delta P_p$, $V'$, and integrating flow to volume ($V$), the constants, $E_l$ and $R_l$ can be calculated from all the available data points. The computerised analysis applies an algorithm to minimise the mean squared error between measured pressure and the pressure
Zero flow points and midvolume points are marked on a time based trace of tidal flow, volume and transpulmonary pressure. Lung mechanics are calculated as shown and described in the text (Section 3.2.1.2.1). Adapted from Davis et al.\textsuperscript{100}

calculated from the equation of motion for each simultaneous flow and volume measurement. A coefficient of determination ($r^2$) is calculated and should be greater than 0.95. Values below this suggest artifacts or the assumption that a single compartment linear model is inappropriate. If necessary the same method can be applied using more complex models of the respiratory system (see Section 6.4.2.2).

### 3.2.2 Equipment and measurement of dynamic mechanics

Dynamic mechanics measurements are reported in Sections;

- 5.1: A pilot study of the effect of cardiopulmonary bypass on respiratory compliance in infants and young children
- 5.4: An assessment of the Dräger transducer tipped catheter for the measurement of dynamic lung mechanics
Simultaneous flow, volume and pressure data were collected using RASP and converted to an ASCII file. The data was imported into Anadat™ Version 5.1 (RHT Infodat, Montreal, Canada) and periods of regular breathing (minimum 8 consecutive breaths) analysed using MLR and a single compartment linear model. Only analyses with an $r^2$ value $\geq 0.95$ were accepted.

3.2.3 The theory of passive respiratory mechanics

This section will be restricted to the theory of the passive mechanics techniques used in this thesis, i.e. the multiple occlusion technique (MOT) and its variant the multiple interrupter technique (MIT) for the measurement of respiratory system compliance and the single breath technique (SBT) for the measurement of respiratory system compliance, resistance and time constant.

3.2.3.1 The multiple occlusion technique (MOT)

This method of measuring $C_n$ was described by Olinsky et al in 1976, who were the first workers to exploit the Hering-Breuer Inflation reflex (HBIR) to measure passive mechanics in infants. Airway occlusions are made to invoke the HBIR resulting in brief periods of muscle relaxation. In the absence of airflow, the pressure throughout the airways equilibrates and, providing no respiratory muscle activity occurs, pressure at the airway opening reflects the elastic recoil pressure of the respiratory system. Changes in airflow, volume and pressure at the airway opening are measured while a series of airway occlusions at different lung volumes are performed (see Figure 3.4a). Occlusion pressures are plotted against lung volume above end expiratory level (EEL). A linear relationship is usually assumed (i.e. that a single compartment model applies) and a straight line of best fit calculated, its slope being $C_n$ (see Figure 3.4b). A negative volume intercept is usual in unparalysed infants and reflects dynamic elevation of FRC. In the original description of the method, occlusions were made during inspiration but they are now more commonly made during the first two thirds of expiration. Occlusions during inspiration and the final part of expiration lead to potentially unreliable estimates of compliance as the pressure plateaux achieved frequently overestimate the elastic recoil pressure of the respiratory system.
Figure 3.4: The multiple occlusion technique

a) Time based trace of volume and pressure showing a mid-expiratory occlusion.

b) Pressure-volume plot constructed from multiple occlusions. \( V = (C_r \cdot P) + \) volume intercept. 

\[ C_r = 138.4 \text{ mL} \cdot \text{kPa}^{-1}, r^2 = 0.99, 95\% \text{ CI} = 129.5 \text{ to } 147.2 \text{ mL} \cdot \text{kPa}^{-1}, \] volume intercept \(-25.5 \text{ mL}\).

Adapted from Fletcher et al. \(^{105}\)

Potential inaccuracies of the multiple occlusion technique relate to:

- Failure to obtain a relaxed equilibration pressure due to:
  - failure to relax with respiratory muscle activity during the occlusion (Figure 3.5a)
  - slow equilibration of pressure such that a plateau is not achieved before the next inspiratory effort or release of the airway occlusion. This is more likely in the presence of airway disease when resistance is high (Figure 3.5b).
Figure 3.5: Potential problems with the multiple occlusion technique

3.5a): Failure to relax during occlusion. 3.5b): Slow equilibration of pressure plateau. 3.5c): Leak around face mask during airway occlusion with loss of pressure plateau and a step up in end expiratory level. 3.5d): Unstable end expiratory level.
• Inaccurate volume measurements due to:
  
  - loss of volume due to leakage during the occlusion. This may be identified by a step up in EEL, following release of the occlusion, with or without loss of pressure during the occlusion (Figure 3.5c). However the latter may be masked by coexistent active expiratory effort.\textsuperscript{101}
  
  - use of an inconsistent EEL which is more likely when the EEL is unstable and the method of data collection precludes use of a single baseline for all occlusions (Figure 3.5d).

3.2.3.2 The multiple interrupter technique (MIT)

Recently it has been demonstrated that multiple occlusions performed throughout a single expiration (Figure 3.6) offer advantages over the MOT.\textsuperscript{102} Data analysis follows the same principles as for the MOT but shorter plateaux are accepted due to pre-existent equilibration of airway pressure. The measured lung volumes all relate to a single EEL, making this method particularly suitable when the EEL is unstable.

The multiple occlusion techniques for the measurement of $C_m$ are applicable to spontaneously breathing and mechanically ventilated infants and have the advantage of not requiring oesophageal manometry to estimate pleural pressure. In addition the relationship between pressure and volume can be inspected for linearity and if necessary the relationship described by a non-linear function.

**Figure 3.6: The multiple interrupter technique**

![Graph of volume and pressure at airway opening over time](image)

Time based trace of volume and pressure at the airway opening.
3.2.3.3 The single breath technique (SBT)

The single breath technique for the measurement of respiratory mechanics was adapted for use in newborns and young children by Le Souëf et al in 1984. The airway is occluded at end inspiration, invoking the HBIR, then released after a brief pressure plateau during which the pressure equilibrates throughout the airways. A passive expiration follows release of the occlusion. Simultaneous measurements of flow, volume and pressure at the airway opening are obtained and a flow-volume curve plotted (Figure 3.7a and b). It is assumed that the respiratory system behaves as a single compartment linear model, with negligible inertance, and is therefore described by the equation;

\[ P = \left( \frac{1}{C_{rs}} \cdot V \right) + (R_{rs} \cdot V') \]

Where \( P \) is pressure, \( V \) is volume and \( V' \) is flow.

During a passive expiration, the applied pressure \( P \) is zero and therefore;

\[ \frac{1}{C_{rs}} \cdot V = -R_{rs} \cdot V' \]

rearranging

\[ \frac{V}{V'} = -R_{rs} \cdot C_{rs} \]

\( C_{rs} \) is calculated by measuring the recoil pressure at the moment of occlusion and extrapolating the flow volume curve to zero flow;

\[ C_{rs} = \frac{\text{Volume above elastic equilibrium volume}}{\text{Plateau pressure at airway opening}} \]

As \( \frac{V}{V'} \) is the slope of the expiratory passive flow volume curve and \( C_{rs} \) is known, \( R_{rs} \) can be calculated.

The important assumptions of the technique can therefore be summarised as;

- pressure equilibrates throughout the airways during the occlusion
- relaxation occurs during the occlusion and expiration is passive
- the respiratory system behaves as a single compartment linear model with unique values for compliance and resistance irrespective of flow or volume
Figure 3.7: The single breath technique

3.7a): Flow-volume curve. 3.7b): Time based trace of flow, volume and pressure. The slope of the flow-volume curve is determined across the linear portion (AB) and the line extrapolated to zero flow (C). $C_{rs}$ is calculated from the volume above elastic equilibrium at the time of airway occlusion (CD) and the plateau pressure during airway occlusion ($\Delta P$). $R_{rs}$ is calculated from $C_{rs}$ and the slope of the flow-volume curve. Adapted from Fletcher et al.\textsuperscript{105}

These assumptions may not always be valid especially in infants with respiratory disease who have raised resistance and high respiratory rates, and in intubated and mechanically ventilated infants.
3.2.4 Equipment and measurement of passive mechanics

Passive respiratory mechanics measurements in spontaneously breathing infants are reported in Sections:

- 4.4: The relationship between respiratory resistance measured using the single breath technique and airway resistance
- 4.5: Respiratory morbidity and respiratory function in the first year of life following repair of oesophageal atresia

Measurements using the MOT during positive pressure ventilation are reported in Section 5.1: A Pilot study of the effect of cardiopulmonary bypass on respiratory compliance in infants and young children.

The equipment used to measure passive mechanics depended on whether whole body plethysmography was being undertaken during the same measurement session. In infants having plethysmography, the plethysmograph shutter and a Fleisch size 0 or 1 PNT were used for the passive occlusion techniques (see Section 3.3.2). In other infants, a Rendell-Baker Soucek face attached to a spring loaded shutter operated by a cable release, and a Fleisch size 0 or 1 PNT was used. The shutter, which incorporated a pressure port for the measurement of pressure at the airway opening, and had an opening/closing time of 0.03 s has been described in detail by Fletcher et al in 1990. In the smallest infants (< 3 kg), a pressure port was fitted to the face mask, which was attached to a Fleisch 0 or Hans Rudolph 0-10 L·min⁻¹ PNT. This was intermittently occluded by sliding a thumb over the distal end, so minimising dead space and resistance in the smallest infants. Equipment characteristics are summarised in Table 3.1. In intubated infants the shutter was connected between the tracheal tube and ventilator circuit (Section 5.1).

All measurements were made during quiet sleep, either natural or sedated depending on the study protocol (see Section 3.6 for further details on measurement conditions).

For the MOT, brief expiratory airway occlusions were performed and held until the pressure at the airway opening reached a plateau. A minimum of 10 occlusions throughout the first two thirds of expiration were made. At least six breaths were allowed between occlusions after the re-establishment of the EEL. All data were
calibrated, displayed and recorded using an IBM compatible PC and RASP software as described in Section 3.1.2.3. A sampling frequency of 50-100 Hz was used depending on the infant’s respiratory rate.

MOT data were analysed using RASP software and applying strict criteria as suggested by Fletcher et al.\textsuperscript{105}

- a pressure plateau at the airway opening of at least 0.1 s in infants with very rapid respiratory rates and at least 0.2 s in other infants, with a standard deviation in occlusion pressure of less than 0.01 kPa during this period
- at least 8 occlusions throughout the first two thirds of expiration
- a span of plateau pressures of at least 0.3 kPa
- a coefficient of determination ($r^2$) of the slope of the regression line of volume on plateau pressure at the airway opening of at least 0.90

The same apparatus was used for the SBT as for the MOT. A minimum of 5 end inspiratory/early expiratory occlusions were performed and held until the pressure at the airway opening had reached a brief plateau. Data were only accepted if the subsequent expiration was passive, with expiratory flow decreasing in an exponential manner. A minimum sampling frequency of 100 Hz was used. Strict criteria for data analysis were applied as suggested by Fletcher et al.\textsuperscript{105}

- a pressure plateau of at least 0.10 s during which period the standard deviation of pressure was less than 0.01 kPa
- a minimum of 5 breaths between occlusions with no evidence of a leak
- a linear expiratory flow-volume curve over at least 50% of expired volume with a coefficient of determination ($r^2$) at least 0.99

### 3.3 Whole body plethysmography

#### 3.3.1 The theory of whole body plethysmography

Whole body plethysmography permits the measurement of functional residual capacity (FRC) and airway resistance. The infant lies inside a rigid, closed container (plethysmograph) and tidal flow, volume and pressure at the airway opening are measured using a pneumotachograph and pressure transducers. The pressure changes occurring within the plethysmograph are also measured. The airway opening is briefly occluded, using a remotely controlled valve, to hold the lungs at constant volume.
The infant makes respiratory efforts against the valve compressing and rarefying the
gas within the lungs. Application of Boyle’s Law allows calculation of the occluded
lung volume.

Boyle’s Law states that when a fixed mass of gas is compressed under isothermal
conditions, its volume is inversely proportional to pressure;

\[ PV = \text{constant} \quad \text{equation 1} \]
\[ P_1V_1 = P_2V_2 \quad \text{equation 2} \]

where subscripts 1 and 2 indicate the original and altered states of the gas.

At FRC \((V_i)\) the pressure within the alveoli \((P_i)\) is equal to barometric pressure \((P_b)\).
(This represents an approximation in the infant as dynamic elevation of end
expiratory volume will raise pressure in the alveoli slightly above \(P_b\).)

During an inspiratory effort against an airway occlusion alveolar pressure will
decrease \((P_2 = P_b - \Delta P)\) and lung volume increase \((V_2 = \text{FRC} + \Delta V)\). Therefore for
inspiratory efforts equation 2 may be re-written as;

\[ P_b \cdot \text{FRC} = (P_b - \Delta P) \cdot (\text{FRC} + \Delta V) \quad \text{equation 3} \]

Rearranging;

\[ P_b \cdot \text{FRC} = (P_b \cdot \text{FRC}) + (P_b \cdot \Delta V) - (\Delta P \cdot \text{FRC}) - (\Delta P \cdot \Delta V) \quad \text{equation 4} \]
\[ 0 = \Delta V(P_b - \Delta P) - (\Delta P \cdot \text{FRC}) \quad \text{equation 5} \]
\[ \text{FRC} = \Delta V(P_b - \Delta P)/ \Delta P \quad \text{equation 6} \]

Since \(\Delta P\) is very small compared with \(P_b\) it is usually omitted therefore;

\[ \text{FRC} \approx P_b(\Delta V/\Delta P) \quad \text{equation 7} \]

The gas in the lung is fully saturated with water vapour which behaves as if it is
incompressible therefore equation 7 is re-written as;

\[ \text{FRC} \approx (\Delta V/\Delta P) \cdot (P_b - P_{H_2O}) \quad \text{equation 8} \]

In practice the actual volume measured includes the apparatus dead space and any
tidal volume above FRC which must be subtracted from the measured occluded
volume to calculate FRC_{pleth}.

Plethysmographic measurement of FRC assumes;
• there is no flow of gas in the airway during occlusion i.e. airway and alveolar
pressure equilibrate. Poor equilibration is more likely in the presence of airway disease.

- pressure changes are equal throughout the pleural space. Chest wall distortion, again more likely in the presence of airway disease, may result in $\Delta P$ not reflecting mean alveolar pressure change.

- pressure/volume changes are limited to intra-thoracic gas. Large intra-abdominal pressure swings in the presence of significant amounts gas in the intestinal tract may lead to inaccuracies.

- changes in pressure and volume are isothermal i.e. no change in temperature occurs. Compression and rarefaction of gas result in heat gain and loss respectively but whether there is any change in temperature depends on how quickly heat is exchanged between the gas and its surrounding container. Heat exchange within the lungs is very rapid such that changes within the lungs are isothermal. However the rate of heat exchange across the walls of the plethysmograph may be insufficient to maintain isothermal conditions i.e. the conditions are adiabatic. Conditions that are partly isothermal and partly adiabatic are described as polytropic. The lower the respiratory rate the less heat is generated and the more likely are isothermal or polytropic rather than adiabatic conditions to occur. To minimise the errors due to adiabatic or polytropic conditions the plethysmograph should be calibrated using a sinusoidal signal at a frequency similar to the infant’s respiratory rate. In addition as polytropic conditions may apply to the occluded gas volume within the apparatus dead space, this should be kept to a minimum.

When an infant breathes quietly within a plethysmograph pressure changes occur throughout the respiratory cycle as a result of gas compression and rarefaction within the lung due to the resistance of airways and changes in the temperature and humidity of the respired gas. If the respired gas is kept at body temperature, pressure and humidity (BTPS conditions) changes in plethysmographic pressure during spontaneous breathing will result only from the effect of airway resistance. Airway resistance can therefore be calculated from simultaneous measurements of flow at the airway opening and plethysmographic pressure while the infant breathes air at BPTS conditions.
Airway resistance \( (R_{sw}) \) is measured by relating the pressure difference between the alveoli \( (P_A) \) and the airway opening \( (P_{sw}) \) to the simultaneous flow through the airways. Therefore;

\[
R_{sw} = \frac{(P_A - P_{sw})}{V'} \quad \text{equation 9}
\]

where \( V' \) is flow.

\( \Delta V_{\text{pleth}} \) is proportional to \( \Delta P_A \), however the plethysmograph pressure signal must be calibrated in terms of absolute pressure before \( R_{sw} \) can be calculated. This is done by deriving a calibration factor that relates changes in \( V_{\text{pleth}} \) to changes in \( P_{sw} \) during an airway occlusion (when \( \Delta P_A \) equals \( \Delta P_{sw} \)). The calibration factor applies only at the lung volume that it is calculated and requires correction based on the anatomical dead space and the inspired tidal volume before \( R_{sw} \) can be calculated.\(^{106}\)

Although plethysmography is very complex and limited to specialised laboratories it has several advantages over other methods of assessing respiratory function;

- it does not assume the mechanical properties of the lungs are described by a single compartment linear model
- it does not require muscle relaxation
- simultaneous measurement of lung size and airway resistance are obtained. The interdependence of the two measurements is critical when determining changes due to disease or therapy\(^{107}\)
- airway resistance is measured throughout the entire respiratory cycle which helps to differentiate the site of airway obstruction\(^{106}\)

### 3.3.2 Plethysmographic equipment and measurements

Whole body plethysmographic measurements are reported in Sections;

- 4.2: The relationship between \( t_{\text{PEFR}} \) and specific airway conductance
- 4.4: The relationship between respiratory resistance measured using the single breath technique and airway resistance
- 4.5: Respiratory morbidity and respiratory function in the first year of life following repair of oesophageal atresia

All measurements were made using a 100 L variable pressure plethysmograph (Figure 3.8), which was calibrated prior to use while containing bags of saline with a
total weight approximately equal to that of the infant. Plethysmograph pressure \( P_\text{pleth} \) was measured using a Validyne MP45 \( \pm 0.2 \) kPa pressure transducer. To approximate pressure changes occurring during measurements, 20 mL of air (40 mL for infants over 4 months of age) were syringed into and out of the chamber at a frequency equivalent to the infant’s respiratory rate and the transducer output calibrated in terms of volume. Airflow was measured using a Fleisch 0 or 1 PNT (attached to a Rendell-Baker Soucek face mask) connected to a Validyne MP45 \( \pm 0.2 \) kPa pressure transducer. Pressure at the airway opening was measured via a port in the mask mount using a Validyne MP45 \( \pm 5 \) kPa pressure transducer. The PNT was connected to a shutter block to permit airway occlusions and switching into a highly compliant 2 L rebreathing bag containing warmed humidified oxygen enriched air for the measurement of \( R_{aw} \). Flow and pressure at the opening were calibrated as described in Section 3.1.2.3.1. The apparatus resistance at a flow of 100 mL·s\(^{-1}\) was 0.78 kPa·L\(^{-1}\)·s using the Fleisch 0 PNT and 0.48 kPa·L\(^{-1}\)·s with the Fleisch 1 PNT, with an apparatus dead space of 7.6 mL and 26 mL respectively. All signals were
sampled at 50-100 Hz (depending on respiratory frequency), digitised, stored and analysed using a computer and RASP software (see Section 3.1.2.3).

Infants were measured after sedation with oral triclofos sodium while in quiet sleep (see Section 3.6.2). The infants were measured supine with the neck slightly extended and the head in the midline, supported by small sandbags. Therapeutic putty was used to achieve an airtight seal around the face mask. The cheeks were supported with latex strapping attached to the mask mount.

All measurements were made after allowing the plethysmograph to reach thermal equilibrium. For FRC_{pleth} measurements, at least 5 early expiratory occlusions were made, after a stable end expiratory level had been established, each being held for 2 to 3 respiratory efforts. FRC_{pleth} was then calculated as the mean of 3 to 5 occlusions. Criteria for accepting data for FRC_{pleth} analysis were:

- no evidence of a leak of gas during the occlusion i.e. no flow through the pneumotachograph and the re-establishment of the end expiratory level post occlusion
- changes in P_{pleth} and P_{ao} were in phase during the occlusions. Poor phasing suggests a leak of air from the apparatus, glottic activity or poor equilibration
- occlusion occurred at or within 10% of the start of expiration

FRC_{pleth} was calculated from the total occluded gas volume by allowing for the volume occluded above end expiratory volume and the apparatus dead space.

For R_{aw} measurements, the infants breathed warmed, humidified, oxygen-enriched air. The temperature was adjusted until a satisfactory plethysmograph pressure-flow loop (crossing at points of zero flow) was obtained. At least three epochs of data, each of 18-36 s depending on sampling frequency, were collected for each infant. The rebreathing bag was flushed between each epoch to minimise accumulation of carbon dioxide. Values of R_{aw} were reported as the mean of between 5 and 25 breaths. R_{aw} was calculated from the beginning and end of both inspiration and expiration, i.e. at 4 points throughout the respiratory cycle, giving initial and end inspiratory and expiratory R_{aw}. The flows used for analysis depended on the specific study protocol and are given in the relevant sections. Breaths for R_{aw} analysis were only accepted if
the pressure-flow loops were closed at the points of zero flow.

Specific airway conductance \( (sG_{aw}) \) was calculated by dividing the reciprocal of \( R_{aw} \) by \( FRC_{pleth} \).

### 3.4 The rapid thoraco-abdominal compression (RTC) technique

#### 3.4.1 The theory of the RTC technique

Expiratory flow limitation is the underlying principal which allows spirometry in older children and adults to make the most sensitive and useful assessment available of airway function. The concept of flow limitation i.e. as transpulmonary pressure is increased beyond a critical level no increase in flow is generated, is widely accepted although there remains uncertainty over the mechanism. Three major theories have been postulated;

- the equal pressure point theory\(^{108}\)
- the Starling resistor theory\(^{109}\)
- the choke point or wave speed theory\(^{110}\)

Forced expiration can be achieved in infancy by externally applied thoraco-abdominal pressure. The technique relies on an inflatable jacket to force expiration at the point of end inspiration during tidal breathing. The aim is to assess airway function by achieving expiratory flow limitation.

The tidal volume forced expiration allows assessment of a partial forced expiratory flow curve. The parameter most often determined is maximal flow at functional residual capacity \( (V'_{max,FRC}) \) (see Figure 3.9). Peak forced expiratory flow is not useful, as it is mainly determined by compression pressure.\(^{111}\) Curve shape as a reflection of airway status has also been assessed by Le Souëf et al.\(^{112}\) These authors reported convex curves (see Figure 3.10) to be more common in normal infants and concave curves to be more common in infants with airway disease. In addition, those infants with flow limitation during tidal expiration, where application of external pressure does not increase expiratory flow, are likely to have more severe airway disease than those without flow limitation on tidal expiration. However these authors also found curve shape to be determined by the compression pressure (applied transpulmonary pressure) making it important that comparisons are made at a standardised compression pressure whether or not flow limitation had been reached.
Figure 3.9: Determination of $V'_{\text{max,FRC}}$

3.9a): Time based recording of flow, volume and jacket pressure during a rapid thoraco-abdominal compression. 3.9b): Flow-volume curve to demonstrate calculation of $V'_{\text{max,FRC}}$. 

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Figure 3.10: RTC flow-volume curves

Examples of flow-volume curves of different shapes. [Le Souèf et al]

The percentage of pressure transmitted across the chest wall from the inflatable jacket to the pleural space varies between jackets, between infants and depending how tightly the jacket is applied. This can be measured using oesophageal manometry or a non-invasive occlusion technique to determine pressure throughout the respiratory system during end inspiratory airway occlusions with and without the jacket inflated.

The advantages of the RTC techniques are that:

- they do not depend on the respiratory system being described by a linear single compartment model
- they are simple compared with whole body plethysmography and non-invasive compared with oesophageal manometry
- they primarily reflect airway calibre upstream of the flow limiting segment i.e. they are far less influenced by upper airways resistance than the other techniques. This is particularly relevant in infants who are preferential nose breathers since nasal resistance may contribute up to 50% of total resistance.
The main limitations of the techniques are that:

- reproducibility of measurements of $V'_{\text{max,FRC}}$ depend on FRC being stable between forced expirations
- there are doubts over whether flow limitation is always achieved. This is more likely to be a problem in healthy infants than in those with airway pathology.

The wide within and between subject variability of $V'_{\text{max,FRC}}$ can result in values within the normal range even when the shape of the flow-volume curve is markedly concave suggesting airway obstruction. As a result it has been suggested that the sensitivity of partial expiratory flow volume curves can be increased by assessing the shape of the curve rather than reporting $V'_{\text{max,FRC}}$ alone.¹¹²

### 3.4.2 Equipment and measurement of $V'_{\text{max,FRC}}$

Measurements using the rapid thoracic compression technique are reported in Section 4.5: Respiratory morbidity and respiratory function in the first year of life following repair of oesophageal atresia.

The apparatus used is shown in Figure 3.11. The jackets were supplied by Hannover Medical School, Germany. They were wrapped around the infant’s chest and abdomen with the arms remaining outside, and fastened using Velcro. The jacket contained an expandable bladder which was inflated through wide bore (3 cm internal diameter) tubing connected to a 50 L gas reservoir. The pressure within the gas

**Figure 3.11: Equipment for the RTC technique**
reservoir was controllable between 0 and 10 kPa. The jacket was inflated and deflated by manually operating a 2-way valve in the tubing connecting the jacket to the gas reservoir. Jacket pressure was measured using a Validyne MP45 ±10 kPa pressure transducer. Flow, volume and pressure at the airway opening were measured using a Rendell-Baker Soucek face mask and Fleisch size 1 PNT as described in Sections 3.1.2.1 and 3.1.2.2.

Infants were measured sedated during quiet sleep (see Section 3.6.2). The inflatable jacket was applied snugly but taking care to avoid too tight an application which could have resulted in changes in respiratory pattern. The face mask was then positioned to allow flow, volume and pressure at the airway opening to be recorded. All data were collected with a real time display of flow, volume and jacket pressure. End inspiratory jacket inflations were made and held until end expiration. An initial jacket pressure of ≈2.5 kPa was used and progressively increased in steps of ≈1 kPa until no further increase in $V'_{\text{max,FRC}}$ was seen or a jacket pressure of 10 kPa was reached. A minimum of 3 satisfactory forced expiratory flow volume curves was obtained at the pressure producing $V'_{\text{max,FRC}}$.

All data were displayed, calibrated, recorded and analysed using RASP software (see Section 3.1.2.3). A sampling frequency of 200 Hz was used. The criteria for accepting data were:

- a smooth expiratory flow-volume curve in the region of FRC
- forced expiration continuing past FRC
- no evidence of an elevated end expiratory level after tidal breathing had stabilized post inflation (as this would have suggested a leak around the face mask)
- jacket reaching a pressure plateau within a 100 ms of the start of inflation
- PEF achieved before 50% of tidal volume expired

$V'_{\text{max,FRC}}$ is reported as the mean and coefficient of variation (i.e. (mean/SD)-100), of 3 satisfactory curves obtained at the lowest compression pressure which achieved the highest flows.
3.5 Body surface measurements

3.5.1 The theory of body surface measurements

In 1967 Konno and Mead\textsuperscript{115} developed the theory of two components of respiratory volume. According to these authors, the "chest wall", in physiological terms, includes all parts of the body outside the lung which share changes in lung volume. Anatomically this "chest wall" is divided, by the costal margin, into two components, the rib cage (RC) and the abdomen (AB). Each component moves as a unit, but the two components can move together or independently, i.e. it is possible to inspire mainly with the abdomen or with the rib cage, or to produce paradoxical movements of the two parts. Konno and Mead demonstrated that in normal subjects, the general relationship between volume and motion change is:

\begin{equation}
\text{Volume} = k_{rc} \text{RC} + k_{ab} \text{AB}
\end{equation}

Where RC and AB are the rib cage and abdominal motion changes and $k_{rc}$ and $k_{ab}$ are the volume motion coefficients, or gains of each transducer, which must be determined by calibration (see below).

The theory of two independent parts has been widely applied to measurements made in the range of tidal volume with two exceptions;

- patients with chronic obstructive pulmonary disease in which it is necessary to take into account a third component, cranio-caudal motion change\textsuperscript{116,117}
- fully paralysed and ventilated patients in whom, as the muscles are inactive, the ribcage and abdomen can be considered to move as a whole and therefore only one transducer is necessary

The first equipment based on the Konno and Mead theory was the magnetometer, which measures motion by determining changes in anteroposterior diameters.\textsuperscript{115} Respiratory Inductance Plethysmography (RIP) which measures motion as the variation in cross-sectional area of the thorax and abdomen was developed by Cohn et al.\textsuperscript{83} RIP has been shown to be less sensitive to changes in position than magnetometers.\textsuperscript{118} RIP was the method chosen for surface measurements in this thesis and will be considered in more detail.

3.5.1.1 The respiratory inductance plethysmograph (RIP)

The respiratory inductance plethysmograph (RIP) consists of elasticated bands
incorporating coils of insulated wire that are wrapped around the rib cage and abdomen. Each coil forms the inductance element of a resonant circuit which is maintained in oscillation. The frequency of oscillation, \( f \), is described by the following equation:

\[
f = \frac{1}{\pi \sqrt{LC}}
\]

Where \( L \) is the inductance and \( C \) is related to circuit capacitance.

A variation in thoracic or abdominal volume modifies the inductance of the coils and thus the frequency of the oscillating circuit. The frequency changes are converted by a frequency-voltage transducer to a signal that is filtered before being ready for display, recording and analysis. When short term changes in end expiratory volume are being monitored, a direct current (DC) circuit is used. However for longer term studies an alternating current (AC) circuit that stabilizes the baseline is preferred. The AC coupled device returns to zero after a time constant. Linearity of the system throughout the range of physiological volumes is due to small changes in frequency with volume compared to the spontaneous frequency of the oscillating circuit.

Calibration has been a major issue in the use of surface measurements and many methods have been developed. All methods are based on the equation describing the general relationship between volume and motion change (equation 1 Section 3.5.1).

There are two general methods for calibration;

i) **The isovolume method** in which the relative RC and AB gains are determined as a first step. As an optional second step the correctly proportional RC and AB electrical gains are multiplied by a constant so that their sum is equal to the volume measured by spirometry or pneumotachography. The first step requires the subject to shift volume voluntarily to and from the RC and AB compartments with the glottis closed. As overall volume remains constant, the volume change attributable to RC motion must be equal and opposite to that attributable to AB motion. A proportionality factor which correctly sets the RC and AB electrical gains is obtained by plotting RC motion against AB motion. The second step of calibration is performed only if absolute values of \( V_t \) are required and necessitates the subject
breathing through a pneumotachograph or spirometer. Note relative changes in $V_t$ can be obtained without performing the second step. This method cannot be used in infants as cooperation is required.

More recently a variant of the isovolume method, but not requiring voluntary manoeuvres, Qualitative Diagnostic Calibration (QDC) has been described.\textsuperscript{89,119} During natural breathing, there are variations in RC and AB amplitudes from breath to breath. If a subject were to breathe at a constant tidal volume then variability of RC and AB displacements as reflected by their standard deviation (SD) can be used to solve the proportionality constant $K$, as follows;

$$\text{Volume} \propto K \text{RC} + \text{AB}$$

$$K = \frac{\text{SD AB}}{\text{SD RC}}$$

Since subjects cannot and do not usually breathe at a constant tidal volume, a statistical approximation is made and breaths are collected over a five minute period and only those breaths which fall within $\pm 1$ SD of the mean are selected for analysis of SD so that $V_t$ can be assumed to be nearly constant. If required a period of breathing with simultaneous pneumotachograph (PNT) and RIP measurements can be used to obtain absolute values.

The potential advantages of QDC in neonates and infants include;

- no need for a PNT if only relative changes in $V_t$ and derived parameters are required
- calibration is not dependent on subject cooperation

ii) \textit{Methods based on simultaneous recordings of tidal volume using a PNT or spirometer and RIP RC and AB signals}. Breaths are selected for analysis in which there is a wide distribution of RC and AB contributions by using breaths with the subject in different postures,\textsuperscript{120} sleep states\textsuperscript{121} or, in adults, by instructing subjects to perform preferential thoracic and abdominal breathing.\textsuperscript{87} Regression methods are used to obtain the best fit for the data.

\textbf{3.5.1.2 Analysis of data from body surface measurements}

Data from body surface measurements are used to measure tidal breathing parameters
and to assess thoraco-abdominal asynchrony. The ribcage and abdominal signals are summed to give a volume signal which may be either qualitatively or quantitatively calibrated. The volume signal may also be differentiated to obtain a flow signal. The volume and flow signals may then be analysed in the same manner as signals from a pneumotachograph to provide tidal breathing parameters (see Section 3.1.3). Recently Stick et al. have suggested calibration may not be necessary for determining respiratory timing parameters including t_{PEF}\:t_E, for epidemiological studies (see Section 4.3).

Several methods of quantifying thoraco-abdominal asynchrony have been documented using both calibrated and uncalibrated body surface measurements. The most commonly used measure is the phase angle, a concept that has arisen from signal processing of electrical sine waves. When two sine waves are shifted in time relative to each other, the shift is quantified by the phase angle which can be measured from an X-Y plot of ribcage and abdominal signals (Lissajous figure) as shown in Figure 3.12. The amplitude of the RC and AB signals does not affect the calculation and therefore the method can be used with uncalibrated data. This method is simple but has two major disadvantages;

• very distorted loops (e.g. figure of eight type loops) cannot be analysed
• no account is taken of the relative contributions of the RC and AB excursions to tidal volume. If the contribution of one compartment is very small, even large phase shifts will have minimal effect on tidal volume.

These problems can be overcome by using more complex methods of quantifying asynchrony based on scalar traces using calibrated AB and RC signals.

3.5.2 RIP equipment and measurements

In this thesis measurements with RIP are made in Sections:

• 4.3: Uncalibrated respiratory inductance plethysmography for the measurement of tidal breathing parameters
• 4.5: Respiratory morbidity and respiratory function in the first year of life following repair of oesophageal atresia

Data were collected using a Respitrace® (model 10.9230, Ambulatory Monitoring Incorporation, New York) with adjustable bands, incorporating inductance coils,
placed around the ribcage and mid abdomen. The Respitrace® has a 15 Hz low pass analog filter. The gains were set to maximum and the output to AC. The analog signals were digitised with a RTI 815 analog-to-digital converter. Sampling frequencies of 100 and 80 Hz were used for neonates and infants respectively. Data were recorded and analysed using a computer and RASP software (see Section 3.1.2.3).

The data analysis software adds the ribcage (RC) and abdomen (AB) signals to give a sum "volume" signal, which is smoothed and differentiated to give RIP "flow" from which tidal breathing parameters including $t_{\text{PEF}}:t_e$ and the phase relationship of the RC and AB signals are calculated based on Lissajous figures (see Section 3.5.1.2). The digital smoothing process is equivalent to applying a low pass filter with a cut off frequency that is adjusted between 6 and 10 Hz. The program also performs analysis of a simultaneous pneumotachograph signal if available.

The RIP analysis software software, which was developed for the purpose of this thesis, was assessed in two ways. Firstly, sample point recognition, the addition of the RIP ribcage and abdomen signals and the calculation of parameters from the PNT flow and RIP "volume" and "flow" signals were checked and found to be correct using an ASCII print-out of data. Secondly, to assess the effect of the digital smoothing during differentiation of the RIP signal on the measurement of $t_{\text{PEF}}:t_e$, tidal breathing data were recorded with the analog signal of the flow transducer integrated with a Validyne FV156 integrator and collected as if it were the RIP abdomen signal of the Respitrace®. The pneumotachograph flow signal and the substituted RIP abdomen signal were both sampled at 80 Hz. An analysis of 30 breaths was performed with the program set to construct the RIP sum "volume" signal with no contribution from the RIP ribcage signal. The mean (SD) $t_{\text{PEF}}:t_e$ measured from the PNT flow signal was 0.116 (0.008) and from the simultaneous substituted RIP signal 0.125 (0.012).

3.6 Measurement conditions

The research studies presented in this thesis were mainly undertaken in the respiratory laboratory, wards and operating theatres of The Great Ormond Street Hospital for Children and in the neonatal unit of the Homerton Hospital, London. All research
Figure 3.12: Measurement of thoraco-abdominal asynchrony

Ribcage (RC) and abdominal (AB) wave forms. 3.12a): In phase. 3.12b): Out of phase. 3.12c): Lissajous figure. The ratio $m/s$ is an index of thoraco-abdominal asynchrony and can be used to calculate the phase angle.

Involving infants had the approval of the relevant Human Research Ethics Committee. Informed parental consent was obtained for all studies and parents were allowed to stay with their child throughout the measurements unless the studies were being performed after induction of general anaesthesia.

3.6.1 Body weight and length
For all studies the subjects naked weight and length were measured and recorded. Crown-heel lengths were measured using an infant stadiometer.\textsuperscript{124}

3.6.2 Sedation and sleep state
Measurements were obtained during behaviourally determined quiet when posture was stable, respirations regular and there were no eye movements.\textsuperscript{125} Where the protocol required sedation, triclofos sodium in a dose of 50-100 mg·kg\textsuperscript{-1} (depending on age and weight) was given orally. Triclofos sodium is closely related to chloral
hydrate (1g of triclofos is pharmacologically equivalent to 660 mg of choral). All sedated infants were monitored with pulse oximetry as a minimum.
4. Respiratory function measurements for epidemiological and clinical outcome studies

A series of studies assessing simpler methods of measuring respiratory function in spontaneously breathing infants is presented. Sections 4.1 - 4.4 are methodological studies into tidal breathing parameters and passive respiratory mechanics using the occlusion techniques. In Section 4.5 a clinical study of infants with surgically treated oesophageal atresia is presented with emphasis on the role of simpler methods of respiratory function testing.

The following publications have resulted from this work:


4.1 The reproducibility of \( t_{\text{PTFE}:t_E} \) in infancy

4.1.1 Introduction and aims

Despite the increasing interest in the measurement of time to reach peak tidal expiratory flow as a proportion of total expiratory time (\( t_{\text{PTFE}:t_E} \)) little is known about factors influencing the within and between-subject variability of these parameters. Although variability of resting breathing patterns is well recognised,\(^{126}\) most authors have reported results from infants based on a limited number of breaths selected during a short epoch of "regular" breathing.\(^{122,127}\) However, the extent to which factors such as sedation and breath number influence within and between-subject variability of \( t_{\text{PTFE}:t_E} \) in infants remains unclear.

The aims of this study were to examine;

- the effects of postnatal age on \( t_{\text{PTFE}:t_E} \)
- the influence of sedation on \( t_{\text{PTFE}:t_E} \)
- how many breaths should be analysed to determine \( t_{\text{PTFE}:t_E} \)
- whether \( t_{\text{PTFE}:t_E} \) should be determined from a single epoch of breathing
- short term within-subject variability of \( t_{\text{PTFE}:t_E} \)

This section describes a series of 5 related studies designed to address these methodological aspects of measuring \( t_{\text{PTFE}:t_E} \). For clarity, the protocol and results for each study have been combined, with all results being discussed at the end of the section.

4.1.2 Materials and methods

4.1.2.1 Subjects

Healthy infants who had been recruited for epidemiological or methodological research were eligible for inclusion in this study. Infants who had received assisted ventilation, those with congenital abnormalities and those with evidence of respiratory, neuromuscular or cardiac disease were excluded.

Between 1989 and 1993, tidal breathing measurements were made in 266 infants (129 male) between the ages of 1 day and 19 months. Sixty two of these infants had been delivered prematurely (mean gestational age 33 weeks (range 29-36 weeks), mean birthweight 1.89 kg (range 1.19-2.39 kg)). The remaining infants were delivered at
between 37 and 43 weeks gestation (mean 40 weeks) with birthweights ranging from 2.45 to 4.60 kg (mean 3.37 kg).

Some infants were studied on more than one occasion or participated in more than one protocol. Consequently, specific details of the subjects are included in each protocol.

4.1.2.2 Measurement methods

All measurements were made using a face mask and pneumotachograph. The dead space of the apparatus was approximately 2 mL·kg⁻¹ for all infants, with resistance at a flow of 100 mL·s⁻¹ ranging from 1.1 kPa·L⁻¹·s in the smallest preterm infants to 0.3 kPa·L⁻¹·s in infants weighing 6 kg or more. Data were collected in discrete 30-120 s epochs. Full details of the measurement methods and data analysis are given in Section 3.1.3.

Measurements in infants less that 44 weeks postconceptional age were always performed during natural, unsedated sleep. Measurements in older infants were frequently obtained following sedation with triclofos given orally. Room temperature was maintained between 22-25 °C during all measurements using a servo controlled air conditioning unit. Most infants were studied in the supine position, although some newborns would only settle in the lateral position. Data analysis was confined to periods of behaviourally determined quiet sleep.

When the infant was in quiet sleep, a thin ring of therapeutic silicone putty (Carters, Wiltshire) was placed around the infant's nose and mouth. A face mask, attached to the pneumotachograph and recording apparatus, was placed over the nose and mouth and the system checked for leaks. Data recording commenced once the infant was breathing quietly through the apparatus. Tidal flow and volume were recorded under resting conditions for a minimum of 5 minutes, with measurements being repeated after a suitable time interval according to the specific protocol.
4.1.3 The effects of postnatal age on $t_{\text{PTFE}}$: $t_E$

It has recently been reported that values of $t_{\text{PTFE}}$: $t_E$ are significantly higher in newborn compared to older infants.\textsuperscript{122} This difference may reflect more marked braking of expiratory flow during the neonatal period in order to maintain a stable lung volume.

4.1.3.1 Methods and subjects

To determine the effect of postnatal age (PNA), estimates of the mean and standard deviation (SD) of $t_{\text{PTFE}}$: $t_E$ were made at different postnatal ages throughout infancy, with results for each infant being based on 20-50 breaths from a minimum of 2 epochs of data. Moving averages were used to highlight age-related changes for the entire group of 266 subjects as well as for term and preterm infants separately.

4.1.3.2 Results

Mean $t_{\text{PTFE}}$: $t_E$ fell rapidly in both preterm and term infants from 0.49 (0.11) during the first 2 weeks of life to 0.34 (0.09) by 5-8 weeks of age, after which average values levelled off. Within-individual variability (i.e. mean within-subject SD of $t_{\text{PTFE}}$: $t_E$) followed a similar pattern, falling from approximately 0.08 in the first 2 weeks of life to 0.05 by 5 weeks postnatal age but remaining similar thereafter. There were no apparent differences in between-infant variability for the term and preterm groups. The between-infant standard deviation of $t_{\text{PTFE}}$: $t_E$ at any given age was approximately 0.09 for the mean values and 0.03 for its standard deviation.
4.1.4 The influence of sedation on \( t_{pTEF:t_E} \)

Measurements of tidal breathing parameters may be undertaken during natural sleep, particularly in the first few weeks of life. However, in older infants or those in whom measurements of lung mechanics or volumes are also performed, sedation is usually required. The potential effects of sedation on \( t_{pTEF:t_E} \) must therefore be determined before meaningful comparisons of data can be made within or between laboratories or within infants at different ages.

Chloral hydrate and its related drug triclofos sodium are frequently used to sedate infants undergoing lung function tests. While the influence of these sedatives on many parameters of infant lung function has been reported previously,\(^{128,129}\) their effect on \( t_{pTEF:t_E} \) is unclear. The aim of this protocol was to determine whether sedation with triclofos sodium in doses normally used for lung function testing has any influence on \( t_{pTEF:t_E} \) in healthy infants during the first 2 months of life.

4.1.4.1 Methods and subjects

Tidal breathing parameters were measured in 72 healthy full term infants between 5-8 weeks postnatal age. Twenty three were studied during natural sleep and the remaining 49 were studied following sedation with triclofos sodium (75 mg·kg\(^{-1}\)). The naturally sleeping infants had been recruited as part of a study investigating the effects of postnatal age on the Hering-Breuer reflex.\(^ {130}\) The sedated infants were undergoing plethysmographic studies as part of a longitudinal epidemiological study.\(^ {131}\) The two studies were comparable with respect to selection criteria, equipment, measurement conditions and techniques.

The mean \( t_{pTEF:t_E} \) (obtained from a minimum of 2 epochs, with between 20 and 50 breaths being analysed for each individual infant) was compared between the sedated and unsedated group using an unpaired t-test and the 95% confidence interval (95% CI) of the mean difference between the groups calculated. Similar comparisons were performed for respiratory frequency \( (f_R) \), tidal volume \( (V_T) \), expiratory time \( (t_E) \) and peak tidal expiratory flow (PTEF).

4.1.4.2 Results

Characteristics of the two groups and the results of tidal breathing analyses are
summarised in Table 4.1.1. There were no significant differences between the groups with respect to sex, birthweight, gestational age, or age, weight and length at time of test.

Mean (SD) $t_{\text{PTEF}}-t_e$ was 0.325 (0.097) in the naturally sleeping infants and 0.322 (0.079) in the sedated infants. The difference between the groups of $-0.003$ (95% CI: $-0.046$, 0.040) was not significant ($p=0.89$).

Sedation had no significant effect on $t_e$ or $f_R$. However, $V_T$ and PTEF were slightly greater in sedated than unsedated infants (mean difference 4.0 mL (95% CI: 1.3, 6.8 mL) and 12.9 mL·s$^{-1}$ (95% CI: 3.7, 21.9 mL·s$^{-1}$) respectively).

Table 4.1.1: Subject details and the effect of sedation on tidal breathing parameters

<table>
<thead>
<tr>
<th></th>
<th>Unsedated (U) mean (SD)</th>
<th>Sedated (S) mean (SD)</th>
<th>Difference (S-U) mean (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>10:13</td>
<td>24:25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.39 (0.39)</td>
<td>3.35 (0.50)</td>
<td>$-0.04$ ($-0.28$, 0.19)</td>
<td></td>
</tr>
<tr>
<td>Age (weeks)</td>
<td>6.4 (0.8)</td>
<td>6.8 (1.0)</td>
<td>0.4 ($-0.1$, 0.8)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.74 (0.48)</td>
<td>4.78 (0.71)</td>
<td>0.04 ($-0.28$, 0.37)</td>
<td></td>
</tr>
<tr>
<td>$t_{\text{PTEF}}-t_e$</td>
<td>0.325 (0.097)</td>
<td>0.322 (0.079)</td>
<td>$-0.003$ ($-0.046$, 0.040)</td>
<td>0.888</td>
</tr>
<tr>
<td>$t_e$ (s)</td>
<td>0.82 (0.18)</td>
<td>0.78 (0.19)</td>
<td>$-0.04$ ($-0.14$, 0.05)</td>
<td>0.323</td>
</tr>
<tr>
<td>$f_R$ (min$^{-1}$)</td>
<td>42.9 (7.3)</td>
<td>45.8 (9.4)</td>
<td>2.9 ($-1.5$, 7.4)</td>
<td>0.191</td>
</tr>
<tr>
<td>$V_T$ (mL)</td>
<td>36.1 (4.8)</td>
<td>40.1 (5.6)</td>
<td>4.0 (1.3, 6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTEF (mL·s$^{-1}$)</td>
<td>67.7 (14.4)</td>
<td>80.5 (18.6)</td>
<td>12.9 (3.7, 21.9)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval of the mean difference between groups
4.1.5 How many breaths should be analysed to determine $t_{PTF:E}$?

Although recording of tidal breathing is potentially the simplest of infant lung function tests to perform, the number of breaths that can be analysed may be limited by the length of time an infant tolerates the face mask and pneumotachograph, the duration of quiet sleep, irregularity of breathing patterns (e.g. sighs, hiccups), the desire to complete more complex lung function tests during the same measurement occasion and, perhaps most importantly, the time taken for analysis particularly if no computerised system is available. Consequently, most authors have based results of $t_{PTF:E}$ on analysis of approximately 10 breaths in each infant.\textsuperscript{122,127} However, the effect of analysing a greater or lesser number of breaths, taken from one or more epochs, on the final estimate of $t_{PTF:E}$ has not been assessed.

The relative importance of the number of breaths averaged to give an overall reading for each infant depends on both the variability between breaths and the context in which the averaged values of $t_{PTF:E}$ are to be used, for example whether to make comparisons between different groups or to classify individuals according to their results. One application has been to determine whether, as a group, those in the lowest tercile of the population distribution are at increased risk of subsequent wheezing illnesses.\textsuperscript{127} The extent to which infants may be misclassified by basing results of $t_{PTF:E}$ on a small number of breaths is unknown.

The aim of this protocol was to investigate the influence of the number of breaths analysed on the estimated mean and standard deviation of $t_{PTF:E}$.

4.1.5.1 Methods and subjects

The optimal number of breaths to analyse within a single epoch of regular breathing was investigated by calculating the mean and standard deviation of $t_{PTF:E}$ in each infant from the longest stretch of consecutive regular breaths available. This was compared to the estimate obtained when fewer breaths were included. These comparisons were made in 55 infants ranging in age from 1-82 weeks, of whom 34 were sedated and 10 had been delivered prematurely.

The homogeneity of variance between breaths within individual infants and any tendency for mean values to change with increasing breath number were investigated.
The mean and standard deviation of $t_{p_{\text{TEF}}:t_E}$ were calculated for each infant from all the
breaths available for that infant (which ranged from 29 to 60). These “best” estimates
were taken to be each infant’s “true” mean and SD in subsequent analyses. Differences
between the “true” values for each infant and the mean and SD obtained from every
breath number between 5 and 29 (the latter being the maximum achieved in every
individual) were then calculated.

These within-infant differences were considered in relation to the between-infant
differences obtained for the total sample of 266 infants (Section 4.1.3) i.e. an SD
between means and between standard deviations of $t_{p_{\text{TEF}}:t_E}$ at any given postnatal age
of 0.09 and 0.03 respectively.

4.1.5.2 Results

Figure 4.1.1 shows how quickly (breath-wise) the “true” means and standard
deviations were approached. As a consequence of the increased within-infant SD in
infants less than 6 weeks of age, there was a tendency for the younger infants to need
more breaths than older infants to approach their “true” mean but less to approach
their “true” SD. It can be seen that by 10 breaths, most infants were within 0.09 of
their “true” mean and within 0.06 of their “true” SD. By 15 breaths these figures had
fallen to 0.06 and 0.04 respectively.

Considered in relation to the variability of $t_{p_{\text{TEF}}:t_E}$ between subjects (i.e. ≈0.09
irrespective of age (Section 4.1.3)), these results imply that use of a limited breath
number may result in a high proportion of infants being misclassified. For example,
the probability of any infant whose “true” $t_{p_{\text{TEF}}:t_E}$ fell on the 10th centile for his/her
age being reported on the 30th centile or above would be 0.13, 0.08, 0.03 and 0.01
when basing the results on 5, 10, 15 and 20 breaths respectively.
Figure 4.1.1: Within-subject variability of $t_{\text{TER:E}}$.

4.1.1a): Absolute differences between mean $t_{\text{TER:E}}$ calculated from between 5 and 29 breaths and the "true" mean (based on up to 60 breaths) in each of 55 infants. 4.1.1b): Absolute differences between SD for $t_{\text{TER:E}}$ based on 5 to 29 breaths and the "true" SD in the same infants.
4.1.6 Should $t_{\text{PTEF}}:t_E$ be recorded from a single epoch?

Recordings of tidal flow and volume in infants indicate that marked changes in breathing pattern can occur over short periods of time. Recordings from a 2 day old fullterm infant clearly demonstrate this phenomenon (Figure 4.1.2). In this infant, the onset of behaviourally determined quiet sleep was accompanied by marked expiratory braking with a mean (SD) value for $t_{\text{PTEF}}:t_E$ of 0.572 (0.103) (Figure 4.1.2a). However, a minute later, while the infant was behaviourally still in quiet sleep with a similar respiratory rate and tidal volume, there had been a dramatic change in the expiratory flow pattern with a marked reduction in mean (SD) $t_{\text{PTEF}}:t_E$ to 0.213 (0.071) (Figure 4.1.2b). This finding raises questions regarding how to determine the most representative estimate of $t_{\text{PTEF}}:t_E$ in any individual infant.

Figure 4.1.2: Variability of breathing pattern in a term neonate

a) Onset of quiet sleep

Time based recordings of tidal flow and volume from a 2 day old infant. 4.1.2a): Shortly after the onset of quiet sleep. 4.1.2b): One minute later. Note marked variability in breathing pattern.

b) 1 minute later

$t_{\text{PTEF}}:t_E = 0.21$
4.1.6.1 Methods and subjects

To determine whether results calculated from a single epoch are representative of those recorded over successive epochs, $t_{PTEF}:t_E$ was calculated in each infant from 5 separate epochs of breathing spanning at least 5 minutes during quiet sleep. Ten breaths were analysed within each epoch and mean $t_{PTEF}:t_E$ calculated for that epoch. Five separate epochs of breathing were obtained from 102 infants less than 6 weeks old and from 99 infants aged between 6 and 81 weeks.

Results for infants above and below 6 weeks postnatal age at time of study were analysed separately. For each age group, paired t-tests were performed on the difference between the first and second epoch within each infant to assess whether there was any bias in readings from the first epoch.

If a single epoch is representative of recordings over successive epochs, then variation within-infants between-epochs will be small in comparison to that between infants. Random effects models\textsuperscript{132} were used to compare the variation between individuals to that between-epochs within-individuals. (95% CI for the percentage of total variation attributable to differences between-epochs were calculated.)

Table 4.1.2: Variability of $t_{PTEF}:t_E$ during 5 successive breathing epochs in healthy infants

<table>
<thead>
<tr>
<th>Epoch number</th>
<th>$t_{PTEF}:t_E$ mean (SD)</th>
<th>&lt;6 weeks (n = 102)</th>
<th>≥6 weeks (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>0.467 (0.120)</td>
<td>0.287 (0.084)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>0.492 (0.123)</td>
<td>0.313 (0.101)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>0.512 (0.126)</td>
<td>0.303 (0.099)</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>0.516 (0.119)</td>
<td>0.310 (0.094)</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>0.499 (0.127)</td>
<td>0.304 (0.098)</td>
<td></td>
</tr>
</tbody>
</table>
4.1.6.2 Results

Table 4.1.2 shows the average $t_{\text{PTE}^2}$ for each epoch in infants, according to age group. There was a tendency for the first readings of $t_{\text{PTE}^2}$ to be lower. The average rise (2nd – 1st epoch) was similar in both age groups being 0.025 (95% CI: 0.005, 0.054: $p=0.0129$) in the younger and 0.026 (0.015, 0.036: $p<0.00005$) in the older infants. Apart from the tendency for the first epoch to give a lower reading, there was no other evidence of any consistent time-related changes in $t_{\text{PTE}^2}$ readings between epochs.

Table 4.1.3: Components of variance

<table>
<thead>
<tr>
<th></th>
<th>&lt;6 weeks (n = 102)</th>
<th>≥6 weeks (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 5 successive epochs</td>
<td>40.8 (35.7, 46.9) %</td>
<td>19.7 (17.2, 22.7) %</td>
</tr>
<tr>
<td>Omitting 1st epoch</td>
<td>35.6 (30.6, 41.9) %</td>
<td>17.1 (14.7, 20.2) %</td>
</tr>
</tbody>
</table>

Table 4.1.3 shows the variance attributable to differences between the 5 epoch readings as a percentage of the total variation. Amongst the younger group more of the total variability was due to differences between epochs than for the older infants. This was observed even when the first epoch was omitted from the analysis.
4.1.7 Short term within-subject variability

Interpretation of the clinical or physiological significance of differences in $t_{\text{PTEF}:t_E}$ either between or within individuals with respect to increasing postnatal age or therapeutic interventions is dependent on some knowledge of the repeatability of these measurements under basal conditions. The aim of this protocol was to assess short term within-subject variability of $t_{\text{PTEF}:t_E}$.

4.1.7.1 Methods and subjects

Paired measurements of $t_{\text{PTEF}:t_E}$ were available from 64 healthy infants (1 day to 62 weeks PNA) of whom 31 had been delivered prematurely, and 26 had been sedated. The second measurement was made a median of 12 minutes (range 5-108 minutes) following the first. In each infant, measurement of $t_{\text{PTEF}:t_E}$ on both occasions was based on 50 breaths collected from several epochs of breathing spanning at least 5 minutes.

Differences between the 1st and 2nd occasions were calculated and the limits of agreement for the difference between the two results determined. Results were analysed for the group as a whole and separately for infants below and above 6 weeks of age respectively.

4.1.7.2 Results

For the group as a whole, there was no significant difference in $t_{\text{PTEF}:t_E}$ between the two observations, the mean (range) difference (2nd – 1st observation) and 95% limits of agreement being 0.006 (–0.201 to 0.251); –0.127, 0.139; respectively (p=0.49).

Figure 4.1.3 shows this difference plotted against the mean of both observations. There was a tendency for variability to increase with increasing mean $t_{\text{PTEF}:t_E}$. When plotted against postnatal age (Figure 4.1.4), it can be seen that the range of differences between the 2 observations tended to be greater in infants less than 6 weeks of age, although this was not statistically significant (p=0.19). The largest discrepancies between the 2 observations occurred in preterm infants studied during the first few weeks of life. The maximum difference observed in any fullterm infant above the age of 6 weeks was 0.075. Results are summarised according to age group in Table 4.1.4.
Figure 4.1.3: Difference between repeat measurements of $t_{\text{PTF}:t_e}$ plotted against mean $t_{\text{PTF}:t_e}$ in 64 healthy infants

The mean difference and 95% limits of agreement are shown.

Figure 4.1.4: Difference between repeat measurements of $t_{\text{PTF}:t_e}$ plotted against postnatal age in 64 healthy infants
### Table 4.1.4: Within-subject variability of $t_{\text{PTE}}:t_E$

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>1st observation mean (SD)</th>
<th>2nd observation mean (SD)</th>
<th>difference 2nd-1st mean (SD)</th>
<th>95% limits of agreement ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>64</td>
<td>0.366 (0.119)</td>
<td>0.372 (0.139)</td>
<td>0.006 (0.068)</td>
<td>-0.127, 0.139</td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>34</td>
<td>0.445 (0.094)</td>
<td>0.461 (0.118)</td>
<td>0.016 (0.084)</td>
<td>-0.149, 0.181</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>30</td>
<td>0.277 (0.073)</td>
<td>0.272 (0.082)</td>
<td>-0.005 (0.042)</td>
<td>-0.087, 0.077</td>
</tr>
</tbody>
</table>

‡ 95% limits of agreement i.e. ±2 SD of the mean within-subject difference.

The mean (SD) difference between the 1st and 2nd observations was 0.007 (0.070) for observations made within 20 minutes of each other (n=49) and 0.003 (0.062) when the 2nd observation was made between 25 and 108 minutes after the first (n=15), with no significant association between the time interval separating observations and the mean difference (p=0.84).
4.1.8 Discussion

Evaluation of tidal expiratory flow patterns as an index of airway obstruction in infants must take account of a number of factors which may influence such patterns, including the postnatal age of the subject. During passive expiration, the elastic recoil pressure of the respiratory system ($P_e$) provides the driving force to overcome the flow resistive pressures of respiratory system. The higher the $P_e$ and the lower the airway resistance, the higher the flows that will be achieved at any given time. Since $P_e$ is highest at end inspiration (a time when airways are also usually well distended) peak tidal expiratory flow should theoretically be observed almost instantaneously at onset of expiration (i.e. $t_{\text{PEF}}:t_e$ would be extremely low). This pattern is, however, rarely observed except in adults who have been trained to relax or in infants in whom muscle relaxation has been induced by end inspiratory occlusion, demonstrating that some braking of expiratory flow is a normal feature of tidal breathing. It has been suggested that the rapid rise to peak tidal expiratory flow observed in adults with airway obstruction may reflect either the early onset of flow limitation during tidal breathing or the progressive loss of post-inspiratory braking of expiratory flow to prevent excessive hyperinflation in the presence of a prolonged time constant. The recent report that phasic diaphragmatic activity ceases abruptly at end inspiration in patients with severe chronic airflow obstruction suggests that $t_{\text{PEF}}:t_e$ probably reflects alterations in the control of breathing in response to underlying mechanics rather than being a direct index of airway size. This relationship is likely to be even more complex in infants, especially during the first weeks of life, when expiratory braking mechanisms and vagally mediated stretch receptor reflexes interact to control end expiratory lung volume and optimise ventilation.

Recordings of diaphragmatic and posterior cricoarytenoid activity during tidal breathing have identified four major respiratory patterns in healthy newborn infants during sleep. Varying degrees of expiratory braking, which may be predominantly due to laryngeal or post-inspiratory diaphragmatic activity, or to a combination of both, commonly alternate with periods of more rapid breathing when modulation of expiratory flow is minimal. The breath to breath variability and brief duration of these different patterns led Kosch et al to suggest that the expression of these patterns
was not merely a reflection of changes in sleep state (which was not formally monitored) but rather reflected the immaturity of the newborn's respiratory control system. It was proposed that laryngeal control of expiratory airflow involved reciprocal action between decreased abductor activity (posterior cricoarytenoid) and activation of laryngeal adductors (e.g. thyroarytenoid), and was accompanied by a late onset of peak expiratory flow on release of such braking. This pattern of breathing (which would give rise to prolonged values of $t_{p_{TEP}}:t_{E}$) would maintain an elevated lung volume and optimise gas exchange until near end expiration while minimising progressive increases in end expiratory level. With increasing postnatal age, the chest wall stiffens and the need to modulate expiratory flow and timing in order to maintain a stable functional residual capacity (FRC) diminishes.

### 4.1.8.1 Effect of postnatal age

The rapid fall in both the absolute values and intra-subject variability of $t_{p_{TEP}}:t_{E}$ observed during the first six weeks of life in this study is consistent with such a pattern of maturation. Values of approximately 0.5 for $t_{p_{TEP}}:t_{E}$ at birth are similar to those previously reported in neonates and reflect the marked expiratory braking that is frequently observed during the first weeks of life. Similarly the high within-subject variability amongst the neonates reflects the wide range of breathing patterns adopted during this period. Lower and more reproducible values of $t_{p_{TEP}}:t_{E}$ could have been obtained had a limited number of breaths with clearly defined peak flow patterns been selected (Figure 4.1.2b). However, in view of our subsequent findings with respect to number of breaths and epochs, this would not have provided representative values for newborn infants.

Mean values of $t_{p_{TEP}}:t_{E}$ of approximately 0.3, as found in the present study in infants over six weeks of age are similar to those previously reported in both healthy infants and adults. The consistency of these values suggest that expiratory braking to maintain a dynamically elevated lung volume, with the associated prolongation of $t_{p_{TEP}}:t_{E}$, diminishes rapidly beyond the neonatal period. Therefore, although any association between airway size and $t_{p_{TEP}}:t_{E}$ is likely to be weak or absent during the first weeks of life, until a stable FRC is established, beyond this period one
might expect this association to be similar to that reported in older children and adults.\textsuperscript{78,137}

4.1.8.2 The effect of sedation

The marked age related changes in $t_{\text{PTEF}}$ reported in this study are unlikely to be explained by the increased use of sedation in older infants. Large doses of chloral hydrate have been reported to cause upper airway obstruction in susceptible subjects due to a loss of abductor activity.\textsuperscript{138} Consequently it is possible that administration of triclofos sodium (a derivative of chloral) might alter the pattern of expiratory flow modulation and hence $t_{\text{PTEF}}$. However, there was no significant difference in $t_{\text{PTEF}}$, $t_e$ or respiratory frequency between a group of naturally sleeping six week old infants and a group of infants of similar age, weight and sex who had been sedated with 75 mg·kg\textsuperscript{-1} of triclofos. The slightly increased $V_i$ and PTEF observed in the sedated infants may reflect slightly warmer environmental temperatures during plethysmographic studies than when infants were measured in a cot. The comparison is confined to full term infants aged between five and eight weeks, since, at this age, simple lung function measurements are feasible without sedation. It is possible that the effect of sedation would be more marked in newborn infants in whom laryngeal braking is likely to be much more common than in older infants. Since infants during the first month of life are not sedated at the hospitals at which the studies were performed, it was not possible to clarify this issue. However, the results of the current study indicate that the observed fall in $t_{\text{PTEF}}$ beyond the neonatal period is unlikely to be due to the increased use of sedation in older infants.

4.1.8.3 Number of breaths and epochs analysed

Standardisation of the number of breaths and epochs used to estimate $t_{\text{PTEF}}$ is needed to allow reports from different centres to be compared. The influence of breath and epoch number on the estimated mean and variability of $t_{\text{PTEF}}$ has been assessed. Computer-assisted analysis of tidal breathing, such as the system used in this study, allows breath by breath analysis of very large numbers of breaths under direct operator control. However, data in the present study were collected in discrete epochs of 30-120 s depending on sampling frequency, thereby limiting the number of consecutive breaths that could be analysed. Both posterior cricoarytenoid and post
inspiratory diaphragmatic activity are known to increase following sighs, which occur fairly frequently during quiet sleep. Hence the 10 breaths immediately following a sigh were excluded from analysis, thereby further limiting the number of consecutive breaths that could be obtained in any given individual. Although any periods of marked irregularity suggestive of a change in sleep state, body movements or hiccups were excluded from analysis, breaths were not selected according to pattern of breathing, since, with computer-assisted analysis, precise timing of peak flow could be identified with greater accuracy than possible using manual analysis. Thus at least 29 consecutive breaths in each of 55 infants were obtained in order to examine random errors in the estimate of $t_{\text{RTEF:T}E}$ arising from the use of a lesser number of breaths. Published studies have commonly reported $t_{\text{RTEF:T}E}$ as the mean of 10 (or even fewer) breaths. These results suggest that, while this may be adequate for infants above six weeks of age, a closer estimate of the true value is likely to be obtained from 15-20 breaths per infant (Figure 4.1.1). Given the increased intra-subject variability observed in neonates, a minimum of 20 breaths and preferably more should be analysed at this age, to reduce random error in the estimate of $t_{\text{RTEF:T}E}$. Martinez et al. showed that healthy infants in the lowest tercile of the population distribution of $t_{\text{RTEF:T}E}$ when measured at approximately three months of age, were more likely to develop wheezing during subsequent respiratory infections. This relationship was stronger in boys and was thought to reflect the relationship between $t_{\text{RTEF:T}E}$ and diminished airway size prior to any respiratory illness (i.e. some congenital predisposition). The data presented here suggest that results based on a limited number of breaths may result in misclassification of a significant proportion of infants into the wrong terciles. This misclassification could result in an underestimate of the strength of any observed associations between $t_{\text{RTEF:T}E}$ and either current airway function or subsequent respiratory morbidity. However, since within-subject variability decreases with increasing postnatal age (Table 4.1.4), the extent to which older infants (i.e. those over 6 weeks of age) might be misclassified by basing results on only 10 breaths may be lower than predicted from the current study.

As previously discussed, patterns of breathing exhibit marked variability, especially in newborn infants. Therefore, estimates of $t_{\text{RTEF:T}E}$ based on a single epoch may not
provide a representative value, even if a large number of breaths have been analysed. Since it may be difficult to consistently obtain more than 10 consecutive breaths in each infant, the effect of increasing the number of epochs on estimates of $t_{r_{p}_{E}}: t_e$ was examined using 10 breaths from each of five separate epochs of breathing. More than 40% of the total variation between infants aged under six weeks was explained by variation within infants between epochs, nearly double that observed in older infants (Table 4.1.3). This again confirms the findings of Kosch et al\textsuperscript{136} with respect to rapid changes in breathing pattern amongst young infants.

There was a tendency for $t_{r_{p}_{E}}: t_e$ to be lower in the first compared to subsequent epochs. This may reflect adaptation by the infant to the increased load imposed following placement of the mask and recording apparatus\textsuperscript{82} with a resulting temporary reduction in the degree of expiratory flow braking. The first epoch was usually, though not invariably, recorded as soon as there was a leak-free seal and behavioural evidence of quiet sleep (i.e. within a couple of minutes of mask placement). It is therefore possible that quiet sleep was less well established during the first compared with subsequent epochs. While it has been suggested that removal of the face mask every 20 s should be employed to minimise carbon dioxide retention, this procedure may in itself cause alterations in sleep state and increase the variability of resting breathing patterns.

Apart from the tendency for first readings of $t_{r_{p}_{E}}: t_e$ to be lower, there was no other evidence of any consistent time related changes in $t_{r_{p}_{E}}: t_e$ readings between epochs. The mean value obtained by reporting the mean of any two epochs was found to be as representative as that achieved by calculating the mean from all five epochs. Recording of a larger number of consecutive breaths in each epoch for all subjects may have reduced the variability observed within infants between epochs, but regrettably was not feasible in a large enough sample of infants. However, it would appear prudent to allow infants to settle for at least a minute after onset of quiet sleep before recording several epochs of breathing, from which $t_{r_{p}_{E}}: t_e$ and other tidal breathing parameters can be calculated.
4.1.8.4 Within-subject variability

Increased variability in $t_{\text{PTEF}}$ in infants aged less than 6 weeks was observed, with repeat measures differing within individuals by as much as 0.251, despite relatively good agreement between group means on each occasion. This is in marked contrast to studies in the older infants in whom the maximum observed difference between two results was 0.075.

Stick et al\textsuperscript{122} reported limits of agreement for repeat measures of $t_{\text{PTEF}}$ after a 2-4 hour interval of $-0.042$ to $0.070$ in newborn infants, when using inductance plethysmography. These limits are considerably narrower than found in the youngest infants in the current study which may reflect a higher degree of selectivity and analysis of a smaller number of breaths. Whether or not the sensitivity and specificity of $t_{\text{PTEF}}$ as an index of airway function can be improved by selecting periods of regular breathing with clearly defined peak flows (i.e. exclusion of breaths with the most marked expiratory braking), has yet to be determined. However, the intrinsic variability of breathing patterns among newborn infants is clearly evident when analysing a large number of breaths and must be borne in mind when attempting to interpret the results.

There were no significant differences between preterm and full term infants during the first week of life with respect to either absolute values of $t_{\text{PTEF}}$ or its variability within or between subjects. However, since all measurements between 1 and 5 weeks postnatal age were on unsedated preterm infants it is not possible to comment on the precise time course of changes in $t_{\text{PTEF}}$ in full term infants during this period. Some simple method of assessing airway function in large numbers of newborn infants prior to discharge from the maternity wards would provide an invaluable epidemiological tool when studying the determinants of early respiratory morbidity. However, the importance of establishing a stable FRC as well as the interdependence between respiratory timing, modulation of expiratory flow and dynamic elevation of end expiratory lung volume, are likely to confound any relationship between $t_{\text{PTEF}}$ and airway function during the first few days of life. This was demonstrated in a recent pilot study, which found that of the 40 healthy infants whose $t_{\text{PTEF}}$ fell into the lowest quartile at birth, only 10 remained within that quartile when measurements
were repeated at 6-12 weeks. The potential usefulness of tidal breathing parameters as an index of airway function during the neonatal period may be limited not only by the high biological variability at this age but also by difficulties in collecting satisfactory data during quiet sleep. Sleep state is an important determinant of $t_{\text{PTFE}}$ especially in neonates in whom active retardation of expiratory flow by laryngeal activity is significantly diminished during active sleep. It is, therefore, desirable to confine periods of data collection to quiet sleep if comparisons are to be made within and between infants. However, during the first few days of life, the lack of any established routine and the brief duration of clearly defined periods of quiet sleep by behavioural criteria are such that technically satisfactory recordings of tidal breathing during quiet sleep may be virtually as time consuming as more complex measurements of respiratory mechanics at this age.

4.1.9 Conclusions

The results from these studies suggest that $t_{\text{PTFE}}$ decreases rapidly during the first few weeks of life, but that sedation with triclofos sodium does not influence the measurement of $t_{\text{PTFE}}$ in healthy babies. The most representative value of $t_{\text{PTFE}}$ will probably be obtained by allowing the infant to settle for a few minutes after positioning the face mask and then recording several epochs of breathing from which 20-50 breaths can be analysed. However, whether any underlying abnormalities of airway function are better reflected by the lowest $t_{\text{PTFE}}$ recorded rather than the average value, has yet to be assessed.

Although $t_{\text{PTFE}}$ can be measured with an acceptable level of repeatability in infants from 6 weeks of age, within-subject variability is considerably higher amongst newborn infants. Further work is required to clarify whether $t_{\text{PTFE}}$ in the neonatal period, estimated either from breaths showing well defined peak flows or from a larger number of unselected breaths, is of any value in predicting airway function and respiratory morbidity in later infancy.
4.2 The relationship between $t_{PTEF:T_E}$ and specific airway conductance

4.2.1 Introduction and aims

Tidal breathing measurements are being increasingly applied to population based studies of the determinants of early respiratory morbidity.\(^{127,141}\) The time taken to achieve peak tidal expiratory flow as a proportion of total expiratory time ($t_{PTEF:T_E}$), when measured in healthy infants in the first 3 months of life, has been shown to be predictive of subsequent wheezing in boys during the first 3 years.\(^{127,141}\) In addition, $t_{PTEF:T_E}$ has been reported to be significantly related to indices of airway size in adults and children.\(^{78,137}\) However, the extent to which this parameter of tidal breathing is associated with established measures of airway function in infants remains unclear.

The aim of this study was to examine the association between $t_{PTEF:T_E}$ and specific airway conductance ($sG_{aw}$), when measured on the same test occasion, in both healthy infants and those with prior physician diagnosed lower respiratory illness (prior LRI) during the first year of life.

4.2.2 Materials and Methods

4.2.2.1 Subjects

Healthy Caucasian infants were recruited shortly after birth from the community as part of an ongoing epidemiological study.\(^{131}\) Infants born before 36 weeks gestation, requiring ventilatory assistance at birth or suffering from major congenital abnormalities were ineligible. Infants with prior physician diagnosed, wheezing associated, LRI were recruited from the wards and outpatient clinics of the Hospitals for Sick Children, London. All infants with prior LRI, except those with major congenital abnormalities, were eligible for study.

4.2.2.2 Study design

Plethysmographic measurements of lung volume and airway resistance and measurements of tidal breathing parameters were undertaken on two occasions in infants recruited to the epidemiological study: between 5 and 13 weeks postnatal age prior to any lower respiratory illness, and at approximately one year of age. Additional measurements were made between 3 and 18 months of age in some infants who participated as healthy subjects in other ongoing studies. If necessary, measurements
were postponed to allow an interval of at least three weeks from the onset of upper respiratory tract illness. Physician diagnosis of wheezing associated LRI (wheezing, bronchiolitis or asthma) in the interval between the first and subsequent measurements was ascertained by retrospective review of the infant's primary medical care record, which was undertaken as soon as possible after the last visit to the laboratory. Similar measurements were performed, on one occasion, in infants with prior LRI when between 3 and 18 months of age.

For the purposes of this study, infants were allocated into one of three groups according to their age and status at the time of lung function testing. Group 1 consisted of healthy infants aged ≤13 weeks at testing, Group 2 of healthy infants aged >13 weeks at testing, and Group 3 of infants aged >13 weeks at testing with prior LRI. Some infants included in Group 1 were also measured when above 3 months of age, and were included in either Group 2 or 3 depending on their status when older. As the purpose of this study was to examine cross-sectional associations between $t_{\text{RTEF-E}}$ and $sG_{aw}$ longitudinal analysis was not undertaken for these infants.

Lung function measurements were made on 241 occasions in 172 infants, during which data for tidal breathing and plethysmographic assessments of functional residual capacity ($\text{FRC}_{\text{pleth}}$) were successfully obtained on all occasions and for airway resistance ($R_{aw}$) on 220 occasions. Failure to measure $R_{aw}$ occurred because the infant awoke before this could be attempted (10 occasions in 10 infants), or before satisfactory data were collected (11 occasions in 11 infants). This mainly occurred in infants aged ≤13 weeks (17 occasions). However, a subsequent successful measurement was obtained in all but 4 of these infants, who failed to attend a further laboratory appointment.

Therefore, complete data for comparison of $t_{\text{RTEF-E}}$ and $sG_{aw}$ were available for 168 infants (94 male) on 220 occasions. Measurements were obtained on 73 occasions in healthy infants aged ≤13 weeks (Group 1), on 68 occasions in healthy infants aged >13 weeks (Group 2) and on 79 occasions in infants with prior LRI aged >13 weeks (Group 3). Of the 73 infants included in Group 1, 39 (53%) and 13 (18%) were included in Groups 2 and 3 respectively as they were measured again when aged more than 13 weeks. Groups 2 and 3 were, however, independent.
4.2.2.3 Measurement methods

All measurements were made with the infant placed supine in a variable pressure infant plethysmograph, following sedation with triclofos sodium given orally. Data were collected, with room temperature controlled at 22-25 °C using a servo controlled air conditioning unit, during behaviourally determined quiet sleep. Once an airtight seal around the face mask had been confirmed, the plethysmograph was closed and the infant allowed to breathe room air while thermal equilibrium was attained. During this time, data for the analysis of tidal breathing parameters were collected in discrete 30-60 s epochs. Once thermal equilibrium was achieved, at least 5 measurements of \( FRC_{\text{pleth}} \) were obtained. Measurements of \( R_{aw} \) were then made while the infant rebreathed warmed, humidified and oxygen enriched air.

The dead space of the apparatus, excluding face mask, was approximately 2-3 mL·kg\(^{-1}\) for all infants. Apparatus resistance, at a flow of 100 mL·s\(^{-1}\), was 0.78 kPa·L\(^{-1}\)·s in the smallest and 0.48 kPa·L\(^{-1}\)·s in older infants. Full details of the equipment are given in Section 3.3.2.

\( FRC_{\text{pleth}} \) and \( R_{aw} \) were calculated as described in Section 3.3.2. \( R_{aw} \) is reported as the mean of up to 25 breaths (minimum 5). \( R_{aw} \) was measured at 50% of peak \( V' \) at both initial inspiration (II) and end expiration (EE). For each infant, the reciprocal of these values was computed to obtain airway conductance (\( G_{aw} \)) and, after further division by \( FRC_{\text{pleth}} \), specific airway conductance (\( sG_{aw} \)).

Tidal breathing parameters were calculated from a minimum of 20 breaths (range 20-50) collected in 2 discrete epochs, \( t_{TTS-TE} \), respiratory rate and total expiratory time (\( t_{E} \)) being reported as the mean and standard deviation (SD). Periods of sighs or coughs were excluded from analysis.

4.2.2.4 Statistical methods

For each infant, data were entered and validated with a double entry system using a database package (Epi-info, version 5.01b, Atlanta) on an IBM compatible PC. Details entered included lung function parameters, as described above, sex, ethnic group, gestational age, birthweight and age, weight, length and symptom status at testing. Maternally reported smoking in pregnancy and the presence of asthma in first degree
relatives, obtained from questionnaire, were also included. Unpaired t-tests and a two sample test for proportions were used to compare baseline characteristics and lung function parameters between sexes within each group and between Groups 2 and 3. Analyses were performed separately for the infants included in Group 1, as measurements performed beyond 13 weeks of age in some of these infants were included in Groups 2 and 3. Data for Groups 2 and 3 were independent and initially analysed together, the effect of status being examined subsequently. Linear interactive modelling was used to examine the extent to which variation in $t_{F25}$ was explained by $FRC_{p}$ and $EE_{sG}$ (GLIM, Royal Statistical Society, London, 1985). The Chi square statistic was used to assess if the infants in the lowest tercile for $EE_{sG}$ were also in the lowest tercile for $t_{F25}$.

### 4.2.3 Results

Details of the infants included in each group are given in Table 4.2.1. The prevalence of a family history of asthma and maternal smoking in pregnancy was 25% and 44% respectively for Group 1 infants. One infant in Group 1 was symptomatic at the time of testing, slightly crusted nostrils being the only abnormal finding on examination.

There were no significant differences between Groups 2 and 3 with respect to sex distribution and age, weight or length at testing. Significantly fewer infants in Group 3 were of Caucasian origin relative to Group 2, reflecting the differing criteria for inclusion for wheezy infants. Mean birthweight and gestational age were significantly lower in Group 3 infants compared to Group 2 (mean difference; (95% CI): -321 g; (-99, -544 g) and -1.8 weeks; (-0.9, -2.6 weeks) respectively). Mothers reported smoking in pregnancy in a significantly higher proportion of Group 3 than Group 2 infants (mean difference; (95% CI): 20%; (4, 36%)). Similarly, a family history of asthma was significantly more prevalent among infants in Group 3 (mean difference; (95% CI): 25%; (11, 40%)). Three infants (5%) in Group 2 were symptomatic at testing, all of whom had minor signs of upper respiratory illness only. Of the 12 infants (15%) in Group 3 reported as symptomatic at testing, 5 had minor signs of an upper respiratory tract infection, while wheeze was present in 7.

Lung function parameters for each group are summarised in Table 4.2.2. Mean
Table 4.2.1: Subject details

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Healthy ≤13 weeks (n=73)</th>
<th>Group 2 Healthy &gt;13 weeks (n=68)</th>
<th>Group 3 Prior LRI &gt;13 weeks (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female</td>
<td>41:32</td>
<td>34:34</td>
<td>49:30</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>97</td>
<td>97</td>
<td>86*</td>
</tr>
<tr>
<td>FH Asthma (%)</td>
<td>25</td>
<td>16</td>
<td>42***</td>
</tr>
<tr>
<td>Antenatal Smoking (%)</td>
<td>44</td>
<td>32</td>
<td>53**</td>
</tr>
<tr>
<td>Symptoms at testing (n)</td>
<td>1</td>
<td>3</td>
<td>12*</td>
</tr>
<tr>
<td>Age (weeks):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.8 (1.3)</td>
<td>50.0 (10.9)</td>
<td>48.5 (15.0)</td>
</tr>
<tr>
<td>Range</td>
<td>5.0-12.6</td>
<td>22.9-72.9</td>
<td>15.1-78.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.0 (0.8)</td>
<td>9.5 (1.4)</td>
<td>9.5 (1.7)</td>
</tr>
<tr>
<td>Range</td>
<td>3.6-8.2</td>
<td>6.1-13.8</td>
<td>3.6-13.4</td>
</tr>
<tr>
<td>Length (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>57.8 (2.6)</td>
<td>75.7 (4.3)</td>
<td>74.5 (5.8)</td>
</tr>
<tr>
<td>Range</td>
<td>52.1-65.1</td>
<td>65.3-83.9</td>
<td>51.6-84.1</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3440 (502)</td>
<td>3437 (495)</td>
<td>3115 (806)**</td>
</tr>
<tr>
<td>Range</td>
<td>2480-4680</td>
<td>2325-4600</td>
<td>864-4210</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40.1 (1.4)</td>
<td>40.1 (1.4)</td>
<td>38.5 (3.3)**</td>
</tr>
<tr>
<td>Range</td>
<td>37-43</td>
<td>36-43</td>
<td>25-42</td>
</tr>
</tbody>
</table>

LRI: wheezing associated lower respiratory illness, FH: family history

p values for differences Group 3 - 2: * = p <0.05, ** = p <0.01, *** = p <0.001

(range) FRC_{pleth} among healthy infants aged ≤13 weeks (Group 1) was 141.4 mL (87.2-203.9). This represented a mean (SD; range) of 28.6 mL·kg⁻¹ (4.7; 16.5-38.4).

Both II and EE sGaw showed marked between subject variability (mean (range): 2.69 s⁻¹·kPa⁻¹ (1.1-6.2) and 2.47 s⁻¹·kPa⁻¹ (0.6-5.8) respectively). Mean (range) t_{PRE}:t_{E}, respiratory frequency and total expiratory time (tE) for Group 1 infants were 0.321 (0.150-0.522), 46.5 breaths·min⁻¹ (30.8-81.6) and 0.76 s (0.37-1.13) respectively.
### Table 4.2.2: Lung function parameters

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Healthy ≤13 weeks</th>
<th>Group 2 Healthy &gt;13 weeks</th>
<th>Group 3 Prior LRI &gt;13 weeks</th>
<th>Group 3 - 2 Mean Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRCpleth (mL)</td>
<td>141.1 (24.8)</td>
<td>262.4 (50.9)</td>
<td>261.9 (61.0)</td>
<td>-0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-19.1, 17.9</td>
</tr>
<tr>
<td>II sGaw (s⁻¹-kPa⁻¹)</td>
<td>2.69 (1.05)</td>
<td>2.22 (0.69)</td>
<td>1.85 (0.88)</td>
<td>-0.37***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.11, -0.63</td>
</tr>
<tr>
<td>EE sGaw (s⁻¹-kPa⁻¹)</td>
<td>2.47 (1.05)</td>
<td>2.04 (0.70)</td>
<td>1.56 (0.77)</td>
<td>-0.48****</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.24, -0.72</td>
</tr>
<tr>
<td>t_{PTEF:T_E}</td>
<td>0.321 (0.075)</td>
<td>0.295 (0.077)</td>
<td>0.257 (0.079)</td>
<td>-0.039***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.013, -0.064</td>
</tr>
<tr>
<td>f_e (breaths·min⁻¹)</td>
<td>46.5 (9.9)</td>
<td>30.5 (3.9)</td>
<td>32.8 (8.4)</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.3, 5.0</td>
</tr>
<tr>
<td>t_e (s)</td>
<td>0.76 (0.18)</td>
<td>1.17 (0.18)</td>
<td>1.13 (0.25)</td>
<td>-0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.12, 0.05</td>
</tr>
</tbody>
</table>

LRI: lower respiratory illness, II sGaw: specific airway conductance at initial inspiration, EE sGaw: specific airway conductance at end expiration

p values for differences Group 3 - 2: *** = p <0.001, **** = p <0.0001

Mean (range) FRCpleth for Groups 2 and 3 was 262.4 mL (158.8-375.6) and 261.9 mL (109.9-435.4) respectively, and this group mean difference (Group 3 – 2) of -0.6 mL was not significant (Table 4.2.2). This represented a mean (SD; range) of 27.8 mL·kg⁻¹ (4.1; 19.7-0.7) in Group 2 and 28.0 mL·kg⁻¹ (7.1; 18.5-63.1) in Group 3. Mean II sGaw, EE sGaw and t_{PTEF:T_E} were significantly lower among Group 3 infants compared to Group 2 (Table 4.2.2). Mean (range) II sGaw for Groups 2 and 3 was 2.22 s⁻¹·kPa⁻¹ (0.8-4.4) and 1.85 s⁻¹·kPa⁻¹ (0.7-5.0), mean (range) EE sGaw was 2.04 s⁻¹·kPa⁻¹ (0.5-4.3) and 1.56 s⁻¹·kPa⁻¹ (0.3-4.2) and mean (range) t_{PTEF:T_E} was 0.295 (0.138-0.500) and 0.257 (0.119-0.469) respectively. There were no significant differences in respiratory rate and t_e between Groups 2 and 3 (Table 4.2.2).
Table 4.2.3: Regression analyses for $t_{\text{PTEF}}:t_E$ in healthy infants $\leq$ 13 weeks of age (Group 1)

<table>
<thead>
<tr>
<th>Regression coefficient (95% CI)</th>
<th>$r^2$</th>
<th>Chi square value (1 degree freedom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II $sG_{sw}$</td>
<td>0.015 (-0.002, 0.03)</td>
<td>0.04</td>
</tr>
<tr>
<td>EE $sG_{sw}$</td>
<td>0.016 (-0.005, 0.03)</td>
<td>0.05</td>
</tr>
<tr>
<td>$FRC_{\text{pleth}}$</td>
<td>0.001 (0.0003, 0.002)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Abbreviations as for Table 4.2.2 ** = $p < 0.01$

The data were then examined within each group to determine whether there were any significant sex differences in gestational age, birthweight, age, weight and length at test as well as lung function parameters ($FRC_{\text{pleth}}, FRC_{\text{pleth}}\cdot\text{kg}^{-1}, t_{\text{PTEF}}:t_E$ and II and EE $sG_{sw}$). Boys and girls in Group 1 were of comparable gestational age and age at testing. Girls in Group 1 were significantly lighter at birth (group mean difference (95% CI): 270 g (42, 500 g); $p=0.02$), lighter at testing (group mean difference (95% CI): 0.6 kg (0.3, 0.9 kg); $p < 0.001$) and shorter at testing (group mean difference (95% CI): 1.8 cm (0.6, 3.0 cm); $p < 0.01$). However, there were no significant sex differences in this group with respect to $FRC_{\text{pleth}}, FRC_{\text{pleth}}\cdot\text{kg}^{-1}, t_{\text{PTEF}}:t_E$ and II and EE $sG_{sw}$. There were no significant sex differences for infants in Group 2. Although of similar age and length at testing to boys, there was a tendency for girls in Group 3 to be lighter than boys (mean difference for boys - girls; 95% CI: 0.54 kg; -0.2, 1.3 kg; $p=0.18$). Therefore, although absolute lung volume was lower in girls (mean difference; (95% CI) boys - girls; 35.7 mL; (8.5, 62.8 mL; $p=0.01$)), $FRC_{\text{pleth}}\cdot\text{kg}^{-1}$ was not significantly different (mean difference; (95% CI); 2.2 mL·kg$^{-1}$; (−1.1, 5.5 mL·kg$^{-1}$ $p=0.18$). Data for boys and girls were therefore pooled within groups for the subsequent analyses.

Using linear regression and with $t_{\text{PTEF}}:t_E$ as the outcome variable, neither II nor EE $sG_{sw}$ were significantly associated with $t_{\text{PTEF}}:t_E$ in Group 1 infants (Table 4.2.3). However, a
Table 4.2.4: Regression analyses for $t_{\text{PTEF}}:t_{\text{E}}$ in older healthy infants (Group 2) and those with prior lower respiratory illness (Group 3)

<table>
<thead>
<tr>
<th>Regression coefficient (95% CI)</th>
<th>$r^2$</th>
<th>Chi square value (1 degree freedom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$II\ sG_{aw}$</td>
<td>0.015</td>
<td>0.11</td>
</tr>
<tr>
<td>($-0.001, 0.03$)</td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>$EE\ sG_{aw}$</td>
<td>0.035</td>
<td>0.04</td>
</tr>
<tr>
<td>(0.018, 0.051)</td>
<td></td>
<td>6.4**</td>
</tr>
<tr>
<td>$FRC_{\text{pleth}}$</td>
<td>0.0003</td>
<td>0.11</td>
</tr>
<tr>
<td>(0.00006, 0.0005)</td>
<td></td>
<td>18.4***</td>
</tr>
</tbody>
</table>

Abbreviations as for Table 4.2.2: ** = $p < 0.01$, *** = $p < 0.001$.

A weak, but significant association was observed between $FRC_{\text{pleth}}$ and $t_{\text{PTEF}}:t_{\text{E}}$, but this explained only a low proportion (11%) of the total variance in $t_{\text{PTEF}}:t_{\text{E}}$ (Figure 4.2.1).

Among the older infants (Groups 2 and 3), a significant but weak association was found between $t_{\text{PTEF}}:t_{\text{E}}$ and both $EE\ sG_{aw}$ and $FRC_{\text{pleth}}$, but not $II\ sG_{aw}$ (Table 4.2.4). The relationship between $t_{\text{PTEF}}:t_{\text{E}}$ and $EE\ sG_{aw}$ for infants in Groups 2 and 3 is shown in Figure 4.2.2, with separate identification of data points for those Group 3 infants who

**Figure 4.2.1: Scattergram of $t_{\text{PTEF}}:t_{\text{E}}$ and $FRC_{\text{pleth}}$ in healthy infants aged 13 weeks or less**
were wheezy at testing. For Group 1 infants being in the lowest tercile for \( t_{PTFE}:t_E \) was not associated with being in the lowest tercile for EE \( sG_{aw} \) (Chi square statistic 2.23, \( p > 0.10 \), Table 4.2.5). For older infants (Groups 2 and 3) being in the lowest tercile for \( t_{PTFE}:t_E \) was associated with being in the lowest tercile for EE \( sG_{aw} \) (Chi square statistic 10.35, \( p < 0.01 \), Table 4.2.5).

Table 4.2.5: Distribution of infants by terciles for EE \( sG_{aw} \) and \( t_{PTFE}:t_E \) for healthy infants \( \leq 13 \) weeks of age (Group 1) and infants \( > 13 \) weeks of age with or without prior lower respiratory illness (Groups 2 and 3)

<table>
<thead>
<tr>
<th></th>
<th>number of infants in lowest tercile for EE ( sG_{aw} )</th>
<th>number of infants not in lowest tercile for EE ( sG_{aw} )</th>
<th>( \chi^2 ) (1 df)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of infants in lowest tercile for ( t_{PTFE}:t_E )</td>
<td>10</td>
<td>13</td>
<td>2.23</td>
</tr>
<tr>
<td>number of infants not in lowest tercile for ( t_{PTFE}:t_E )</td>
<td>13</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td><strong>Groups 2 and 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of infants in lowest tercile for ( t_{PTFE}:t_E )</td>
<td>25</td>
<td>24</td>
<td>10.35**</td>
</tr>
<tr>
<td>number of infants not in lowest tercile for ( t_{PTFE}:t_E )</td>
<td>24</td>
<td>74</td>
<td></td>
</tr>
</tbody>
</table>

EE \( sG_{aw} \): specific airway conductance at end expiration, \( \chi^2 \): chi square statistic, ** = \( p < 0.01 \).
4.2.4 Discussion
Tidal expiratory flow patterns in infancy may reflect both age (Section 4.1) and underlying lung mechanics. During passive expiration, the elastic recoil pressure of the respiratory system is highest at onset of expiration, a time when the airways are also well distended and hence resistance relatively low. Theoretically, peak tidal expiratory flow should therefore occur at onset of expiration, giving rise to a low $t_{\text{PEF}-t_E}$. In infants, this pattern may be evoked by inducing muscle relaxation with a brief end inspiratory occlusion, but is otherwise unusual, indicating that some braking of tidal expiration is normal. It has been suggested that the low values of $t_{\text{PEF}-t_E}$ observed in adults with airway obstruction reflect alterations in control of breathing, with a reduction of expiratory airflow braking in response to underlying respiratory mechanics, rather than being simply a direct index of lower airway size.\textsuperscript{78}

In this study, measurements of $t_{\text{PEF}-t_E}$, FRC\textsubscript{pleth} and airway resistance were made on the same test occasion in healthy infants and those with prior physician diagnosed wheezing.
associated LRI. Group mean $t_{\text{PREF}}:t_E$ in the younger healthy infants was comparable to that reported by Martinez et al for a group of infants of similar age.\textsuperscript{127} Among the older infants, mean $t_{\text{PREF}}:t_E$ was significantly lower in the group with prior LRI, most of whom were asymptomatic at testing, when compared to a group of healthy infants of a similar age. A lower $t_{\text{PREF}}:t_E$ has also been reported in adults with airflow obstruction\textsuperscript{78} and in infants with bronchopulmonary dysplasia,\textsuperscript{79} but was not observed in asthmatic children who were asymptomatic at testing.\textsuperscript{137} The data reported here shows that, although group mean $t_{\text{PREF}}:t_E$ was significantly lower in infants with prior LRI, there was considerable between subject variation, suggesting that $t_{\text{PREF}}:t_E$ may discriminate between groups but not between individuals. Martinez et al have shown that infants with a $t_{\text{PREF}}:t_E$ in the lower tercile of the distribution, when measured before 13 weeks of age, are at significantly greater risk of developing wheezing associated LRI by 3 years of age.* \textsuperscript{141}

However, the purpose of this study was to report cross-sectional associations of $t_{\text{PREF}}:t_E$ with an established measure of airway function, ($sG_{aw}$) analysis of the longitudinal data not being feasible until all follow up studies have been completed.

In this study, group mean II and EE $sG_{aw}$ were significantly lower in infants with prior wheezing LRI when compared to healthy infants of a similar age. However, within each group there was considerable between infant variation. The range of values observed in healthy infants in this study is greater than previously reported by Stocks et al.\textsuperscript{142} This may reflect differences in technique, as measurements made by Stocks et al\textsuperscript{142} were undertaken after more prolonged periods of rebreathing than is current practice.

$t_{\text{PREF}}:t_E$ has been reported to be significantly associated with inspiratory $sG_{aw}$ in healthy adults and those with airflow obstruction,\textsuperscript{78} with FEV$_1$ in healthy and asthmatic children (the latter asymptomatic at testing)\textsuperscript{137} and with $V'_{\text{max,FRC}}$ in healthy infants and those with bronchopulmonary dysplasia.\textsuperscript{79} The current study shows that, in healthy infants aged 13 weeks or less, FRC$_{\text{pleth}}$ but not II or EE $sG_{aw}$, is significantly but weakly associated with $t_{\text{PREF}}:t_E$. The lack of a significant relationship between $t_{\text{PREF}}:t_E$ and both II and EE $sG_{aw}$ in younger healthy infants suggests that, in the absence of airflow obstruction, there is relative freedom to vary tidal expiratory flow patterns. Laryngeal and post inspiratory diaphragmatic braking, which are accompanied by late onset of peak expiratory flow and hence prolongation of $t_{\text{PREF}}:t_E$, help to maintain a dynamically

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Figure 4.2.3: The relationship between tidal breathing pattern and specific airway conductance

Scattergram of percentage of expiratory volume at peak tidal expiratory flow ($\Delta V/V$) and inspiratory specific airway conductance ($sG_{aw}$) in healthy adults and adults with lung disease. Adapted from Morris and Lane.78

Elevated FRC and maximize gas exchange in newborn infants. The weak relationship between FRC$_{pleth}$ and $t_{PRE}:t_E$ observed among the younger healthy infants in this study suggests that this phenomenon may persist to some extent throughout the first 3 months of life. The importance of establishing a stable FRC, together with interdependence between respiratory timing, modulation of expiratory flow and dynamic elevation of lung volume, may confound any relationship between $t_{PRE}:t_E$ and indices of airway function, especially in healthy infants. With increasing postnatal age, the need to modulate expiratory flow and timing to maintain a stable FRC diminishes.

In older infants, whether healthy or with prior LRI, EE $sG_{aw}$ was most strongly associated with $t_{PRE}:t_E$. The association with FRC$_{pleth}$ was weaker and was no longer
significant after allowing for sex, and age, length and weight at testing. However, EE $sG_{aw}$ explained only a low proportion of the total variance in $t_{PTEF}:t_E$. This relationship was not significantly different for infants with prior LRI compared to healthy infants. While Morris and Lane\(^{28}\) have found that the percentage of expiratory volume expired at peak tidal expiratory flow is significantly associated with inspiratory $sG_{aw}$ in healthy adults and those with airflow obstruction, the published data (Figure 4.2.3) suggest that this relationship may have been influenced by individuals with $sG_{aw}$ of less than 0.1 s\(^{-1}\)cm H\(_2\)O\(^{-1}\) (equivalent to $\approx$1.0 s\(^{-1}\)kPa\(^{-1}\)), those with values greater than this showing both higher mean values and greater variability in $t_{PTEF}:t_E$. While direct comparisons are impossible, since measurements in infants include a variable component due to the resistance of the nasal passages,\(^{114}\) mean $sG_{aw}$ does appear to be relatively constant from the end of the first year of life to adulthood.\(^{142}\) In the current study, all but 3 of the healthy infants had values of EE $sG_{aw}$ $\geq$1.0 s\(^{-1}\)kPa\(^{-1}\), as did a large proportion of those with prior LRI, reflecting the fact that most of these infants were asymptomatic at testing. In the absence of current airflow obstruction, there should be relative freedom to vary tidal expiratory flow patterns and hence no strong relationship between $t_{PTEF}:t_E$ and other measures of airway function would be expected. Had measurements been confined to only those infants with more severe degrees of airflow obstruction, as evidenced by a low $sG_{aw}$, a stronger relationship might have been found, as indicated by inspection of the data in the current study from infants with $sG_{aw}$ $<$1.0 s\(^{-1}\)kPa\(^{-1}\) (Figure 4.2.2).

### 4.2.5 Conclusions

Measurements of $t_{PTEF}:t_E$, II and EE $sG_{aw}$ in both healthy infants and those with prior wheezing LRI above 3 months of age have shown that both $t_{PTEF}:t_E$ and $sG_{aw}$ are significantly lower in the wheezy compared to the healthy group. There is a significant though weak association between $t_{PTEF}:t_E$ and EE $sG_{aw}$ in infants over 3 months, irrespective of prior wheezing status. However, this association is not significant in healthy younger infants, in whom the pattern of expiratory flow may reflect dynamic maintenance of FRC as much as a response to airway calibre.
4.3 Uncalibrated respiratory inductance plethysmography for the measurement of tidal breathing parameters

4.3.1 Introduction and aims

In 1992, Stick et al. suggested that the measurement of time to reach peak tidal expiratory flow as a ratio of total expiratory time \((t_{PEF}:t_E)\) could be simplified by using uncalibrated respiratory inductance plethysmography (RIP, Respitrace®), which potentially overcomes the need to use a face mask and may avoid the need for sedation in many infants. Their work was based on a study of newborns. However, tidal breathing measurements for epidemiological studies may be more helpful in later infancy, when the values are more reproducible (see Section 4.1).

The aim of this study was to assess the accuracy of uncalibrated respiratory inductance plethysmography for the computerised measurement of \(t_{PEF}:t_E\) in both newborns and infants.

4.3.2 Materials and methods

4.3.2.1 Subjects

Thirty two healthy neonates, 35 healthy infants over 4 weeks of age and 28 infants with physician diagnosed recurrent wheeze were studied. Subject details are summarised in Table 4.3.1. Subjects were classified as preterm if they were born before 37 weeks gestation.

<table>
<thead>
<tr>
<th>Table 4.3.1: Subject details</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
</tr>
<tr>
<td>(n)</td>
</tr>
<tr>
<td>Healthy neonates</td>
</tr>
<tr>
<td>Healthy infants</td>
</tr>
<tr>
<td>Infants with recurrent wheeze</td>
</tr>
</tbody>
</table>

* less than 37 weeks gestation
All healthy subjects were free of cardiorespiratory abnormalities, had no history of wheeze or lower respiratory tract infection and had not required respiratory support other than face mask oxygen in the delivery room. Only 7 of the 28 infants with recurrent wheeze were symptomatic at the time of study. The healthy term neonates were recruited for the evaluation of RIP alone and the remaining subjects were participating in ongoing epidemiological and methodological research studies. Where a subject had serial measurements as part of a longitudinal study, only the first set of measurements was included.

### 4.3.2.2 Study design

In order to assess the agreement between the two techniques for the measurement of \( t_{PTE}/t_{E} \), subjects were studied simultaneously using RIP and a pneumotachograph with face mask. A minimum of three 21-27 second epochs of data were recorded for each subject (epoch length was determined by sampling frequency which was 80 or 100 Hz for infants and neonates respectively). All measurements were made during behaviourally determined quiet sleep,\(^{125}\) with the infants loosely clothed and either supine or semi-recumbent. The neonates were studied unsedated but the majority of the healthy infants and all the infants with recurrent wheeze were sedated with triclofos sodium 50-100 mg kg\(^{-1}\).

**Figure 4.3.1: Example of satisfactory RIP data**

![Example of satisfactory RIP data](image)

\[
\text{Ribcage, Abdomen, RIP "flow", PNT flow}
\]

\[
\text{time s}
\]

\[
\uparrow \text{insp.}
\]

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4.3.2.3 Measurement methods

For each subject, a total of 30 breaths from at least two epochs of data were analysed. Runs of at least 8 consecutive breaths were used. Sighs and the first 10 breaths after a sigh were excluded. Tidal breathing parameters and the phase relationship of the RIP ribcage and abdomen signals were calculated. Full details of the measurement methods and data analysis are given in Sections 3.1.3 and 3.5.2.

4.3.2.4 Statistical methods

Agreement between the two methods of measuring tidal breathing parameters was assessed using the methods of Bland and Altman.\(^\text{133}\)

4.3.3 Results

Satisfactory data using the pneumotachograph (PNT) were obtained in all subjects. Nine subjects (1 of 32 healthy neonates, 4 of 35 healthy infants and 4 of 28 infants with recurrent wheeze) were excluded from the comparison of the two methods because the RIP “flow” signal appeared noisy with multiple peaks during expiration. In five of these infants this may have been due to the summing of RC and AB signals that were out of phase or of very different shapes. An example of satisfactory RIP data is shown in Figure 4.3.1.

<table>
<thead>
<tr>
<th>Subject group</th>
<th>(t_{\text{PTEF}^{\text{TEF}}_{1E}}) PNT mean (range)</th>
<th>(t_{\text{PTEF}^{\text{TEF}}_{1E}}) RIP mean (range)</th>
<th>Difference (PNT-RIP) mean (95% CI)</th>
<th>95% limits of agreement (\pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates (n=31)</td>
<td>0.455 (0.201, 0.748)</td>
<td>0.400 (0.203, 0.713)</td>
<td>0.055 (0.039, 0.070)</td>
<td>-0.032, 0.142</td>
</tr>
<tr>
<td>Healthy infants (n=31)</td>
<td>0.263 (0.135, 0.435)</td>
<td>0.265 (0.103, 0.577)</td>
<td>-0.002 (-0.028, 0.024)</td>
<td>-0.147, 0.144</td>
</tr>
<tr>
<td>Infants with recurrent wheeze (n=24)</td>
<td>0.232 (0.123, 0.459)</td>
<td>0.207 (0.085, 0.423)</td>
<td>0.025 (-0.018, 0.067)</td>
<td>-0.182, 0.232</td>
</tr>
</tbody>
</table>

\(\uparrow\) 95% limits of agreement i.e. \(\pm\)2SD of the mean between method difference

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Table 4.3.3: Within-subject agreement between simultaneous measurements of expiratory time ($t_e$) determined using a PNT and RIP

<table>
<thead>
<tr>
<th>Subject group</th>
<th>$t_e$ PNT (range)</th>
<th>$t_e$ RIP (range)</th>
<th>Difference (PNT-RIP) mean (95% CI)</th>
<th>95% limits of agreement ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates (n=31)</td>
<td>0.57 (0.34, 1.01)</td>
<td>0.56 (0.33, 1.00)</td>
<td>0.01 (+0.00, 0.01)</td>
<td>-0.01, 0.03</td>
</tr>
<tr>
<td>Healthy infants (n=31)</td>
<td>1.01 (0.49, 1.83)</td>
<td>1.02 (0.46, 1.94)</td>
<td>-0.01 (-0.02, +0.00)</td>
<td>-0.07, 0.05</td>
</tr>
<tr>
<td>Infants with recurrent wheeze (n=24)</td>
<td>1.09 (0.52, 1.39)</td>
<td>1.08 (0.52, 1.37)</td>
<td>+0.00 (-0.01, 0.02)</td>
<td>-0.07, 0.08</td>
</tr>
</tbody>
</table>

$t_e$ is in seconds, ² 95% limits of agreement i.e. ±2 SD of the mean between method difference

The group mean (SD) values of $t_{PTE}$-$t_e$ determined using a PNT were 0.455 (0.129), 0.263 (0.077) and 0.232 (0.089) for the neonates, healthy infants and infants with recurrent wheeze respectively. RIP gave mean (SD) values that were 0.055 (0.044) and 0.025 (0.041) lower than the PNT in the neonates and infants with recurrent wheeze respectively, and 0.002 (0.073) higher in the healthy infants over 4 weeks of age. The difference between $t_{PTE}$-$t_e$ determined using a pneumotachograph and RIP for each subject is shown plotted as described by Bland and Altman in Figure 4.3.2, with the 95% limits of agreement for the three groups of subjects given in Table 4.3.2. Large individual differences in many subjects resulted in wide limits of agreement especially in infants beyond the neonatal period. The mean (SD) difference between the expiratory time ($t_e$) determined using a pneumotachograph and RIP were however very small, being +0.009 (0.011), -0.008 (0.031) and +0.005 (0.035) seconds for neonates, healthy infants and infants with recurrent wheeze respectively (Table 4.3.3).

Martinez et al have suggested that healthy infants whose $t_{PTE}$-$t_e$ values are in the lowest tercile have an increased risk of developing wheezing illness. We therefore assessed the degree to which healthy neonates and infants might be misclassified into the lowest tercile by using RIP instead of a PNT to determine $t_{PTE}$-$t_e$. The group of 31
neonates and the group of 31 healthy infants were each ranked according to the value of $t_{\text{PTEF}:t_{\text{E}}}$ determined using a PNT and using RIP. The 10 neonates with the lowest values of $t_{\text{PTEF}:t_{\text{E}}}$ determined with the PNT, were the same 10 neonates with the lowest values of $t_{\text{PTEF}:t_{\text{E}}}$ determined by RIP. Only 6 of the 10 healthy infants with the lowest values of $t_{\text{PTEF}:t_{\text{E}}}$ determined by PNT were amongst the 10 infants with the lowest values determined by RIP.

Figure 4.3.2: Comparison of uncalibrated RIP and a PNT for the measurement of $t_{\text{PTEF}:t_{\text{E}}}$

Difference in $t_{\text{PTEF}:t_{\text{E}}}$ [PNT – RIP] plotted against the mean $t_{\text{PTEF}:t_{\text{E}}}$ determined using a PNT and RIP.
The influence of the phase relationship of the ribcage and abdominal signals was assessed by plotting the difference in $t_{\text{PTFE}} - t_E$ measured using the two methods against the phase angle (Figure 4.3.3). The phase angle ranged from −1 to 54° for healthy neonates, −40 to 57° for healthy infants and −28 to 107° for infants with recurrent wheeze. There was no clear relationship between this measure of asynchrony and the difference in $t_{\text{PTFE}} - t_E$ determined with the two methods.

Figure 4.3.3: Difference in $t_{\text{PTFE}} - t_E$ measured with uncalibrated RIP and a PNT plotted against phase angle
4.3.4 Discussion

Uncalibrated respiratory inductance plethysmography has been compared with a face mask and pneumotachograph for the simultaneous computerised measurement of $t_{pTE}$ in healthy neonates and infants, as well as a group of infants with physician diagnosed recurrent wheeze. The mean (SD) values of $t_{pTE}$ measured using a pneumotachograph were 0.455 (0.129) and 0.263 (0.077) for healthy neonates and infants over 4 weeks of age respectively, which are similar to previously reported values.\(^{122,127}\)

There was a poorer level of agreement between $t_{pTE}$ measured with a PNT and RIP in the current study than was reported by Stick et al.\(^{122}\) in a group of 15 healthy neonates (mean difference (PNT – RIP) –0.014, 95% limits of agreement –0.070, 0.042). However, despite the wider limits of agreement and the large bias between the two methods in the neonates in our study (mean difference 0.055, 95% confidence intervals 0.039, 0.070) the same neonates were classified as being in the lowest tercile for $t_{pTE}$ with the two methods of measurement. The large discrepancies were mainly accounted for by errors in the measurements of time to peak expiratory flow as there was good agreement between the two methods for the determination of expiratory time (Table 4.3.3).

The major differences between this study and that previously published by Stick et al.\(^{122}\) are the use of different analysis software and different criteria for breath selection. Stick et al used a differentiated RIP “flow” signal generated by the Respitrace® with the gains for the ribcage and abdominal signals set at maximum. The Respitrace® model available for this study did not provide a differentiated signal, therefore the ribcage and abdomen signals were both recorded and then added and differentiated using RASP software. Assessment of the software showed a slight over-estimate of $t_{pTE}$ using RIP (0.009) (see Section 3.5.2) but the discrepancy was small and did not explain the differences between $t_{pTE}$ determined with the two methods. The use of a computer program to identify peak expiratory flow should be advantageous in large epidemiological studies as it reduces observer bias. However, the exclusion of breaths without a clearly defined peak expiratory flow may have contributed to the better agreement between the two methods found by Stick et al. The other difference between this study and previous work is that this study includes infants over a wider age range.
Measurements after the neonatal period may be of greater relevance to epidemiological studies as $t_{PTEF} \cdot t_E$ is more reproducible in older infants (Section 4.1) and values of $t_{PTEF} \cdot t_E$ in the neonatal period have not yet been shown to be predictive of future respiratory morbidity.

The assumption underlying the use of uncalibrated respiratory inductance plethysmography for the measurement of $t_{PTEF} \cdot t_E$ in epidemiological studies is that healthy subjects have synchronous ribcage and abdominal movement. Although examination of phase angle failed to identify infants in whom the agreement of the two methods was poor, examination of the RIP ribcage and abdomen signals revealed that many healthy subjects, while appearing clinically in phase showed marked variations in the shape of the ribcage and abdominal signals during early expiration (Figure 4.3.4). In these circumstances one would only expect agreement if the ribcage and abdominal weighting of the sum signal was correct (i.e. the Respitrace® was at least qualitatively calibrated). The exclusion of breaths without a well defined RIP peak expiratory flow by Stick et al may have resulted in the preferential selection of breaths in which the ribcage and abdominal signals are most similar in shape during early expiration.

The mean (SD) percentage contribution of the ribcage to tidal volume changes has been reported as 34 (9)% in young infants increasing to 60 (17)% by 9 months of age which is similar to that seen in adolescents and adults. This large between-subject variability reduces the accuracy with which the relative contribution of the ribcage may be predicted in any individual. Therefore weighting of the two signals such that they each give a fixed proportion of the sum signal is no more likely to yield satisfactory results. The differences in the shape of the ribcage and abdominal signal in early expiration limit the accuracy of uncalibrated RIP for the measurement of $t_{PTEF} \cdot t_E$. Several methods of calibration have been described involving changes in body position or sleep state or periods of simultaneous measurement with a pneumotachograph or spirometer. The application of these calibration methods could negate any advantages of using RIP for the measurement of tidal breathing parameters in epidemiological studies. A recently described method, qualitative diagnostic calibration (QDC) (Section 3.5.1.1) that is performed during tidal breathing without postural or sleep state changes may improve the accuracy of RIP for the measurement of tidal breathing parameters.
Figure 4.3.4: Examples of RIP ribcage and abdominal signals to illustrate marked differences in the shape of the expiratory waveform in healthy infants

a)

Ribcage

Abdomen

↑ insp.

↓ exp.

b)

Ribcage

Abdomen

c)

Ribcage

Abdomen
d)

Ribcage

Abdomen

time (s)

respiratory timing without making the method too complicated for use in epidemiological studies. However, it is possible that diaphragmatic and laryngeal expiratory flow modulation have differing effects on the signals recorded at the surface and at the airway opening and that this would limit the agreement between the two methods even if RIP was calibrated.

4.3.5 Conclusions

The computerised measurement of $t_{\text{PTFE}:T_E}$ using uncalibrated respiratory inductance plethysmography should be used with caution particularly outside the neonatal period. The problems may be greatest in infants who have had respiratory problems even if they are asymptomatic at the time of testing. Examination of the separate ribcage and abdominal signals of healthy infants suggests that some form of qualitative calibration may be desirable if respiratory inductance plethysmography is to be used to determine $t_{\text{PTFE}:T_E}$.

Although Stick et al\cite{Stick1983} used computerised data collection, their analysis required the user to identify peak expiratory flow and the start and end of expiration using cursors. Computerisation of data analysis would make the method more applicable to large population based studies and may reduce observer bias.
4.4 The relationship between respiratory resistance measured using the single breath technique and airway resistance

4.4.1 Introduction and aims

Plethysmographic measurements of lung volume \(FRC_{\text{pleth}}\) and airway resistance \(R_{aw}\) may be used to identify functional and developmental abnormalities in infants.\(^{147-152}\) However, the complexity of these tests limits their epidemiological and clinical applications. The single breath technique (SBT) which measures the resistance, compliance and time constant of the respiratory system during passive expiration following brief airway occlusions is simple and rapid to perform, and is being increasingly applied in clinical settings.\(^{153-156}\) Despite its increasing popularity, the relationship between SBT measurements of total respiratory resistance \(R_{nt}\), which includes chest wall and lung tissue components, and those of airway resistance has yet to be fully established in infants.

The aim of this study was to compare measurements of airway and total respiratory resistance obtained on the same occasion in both healthy infants and those with prior airway disease.

4.4.2 Materials and methods

4.4.2.1 Subjects

Measurements of airway resistance \(R_{aw}\) and total respiratory resistance \(R_{nt}\) were attempted on 135 occasions in 107 infants. Infants were recruited to the study from two sources. Healthy infants were recruited shortly after birth as part of an ongoing epidemiological study.\(^{131}\) Caucasian infants with a gestational age of at least 36 weeks, without major congenital, respiratory, neuromuscular or cardiac abnormalities and who did not require ventilatory support during the neonatal period were eligible for inclusion. Initial measurements were made between 5 and 13 weeks of age, prior to any respiratory illness and, when possible, repeated at around one year of age. Some infants participated in additional measurements between 3 and 18 months of age for other studies.\(^{157}\) Following the last laboratory visit, the primary medical care record of each infant was examined, and any episodes of physician diagnosed wheeze noted.
Measurements were also made, on one occasion, in infants with physician diagnosed recurrent wheezing, recruited from the wards and clinics of the Hospitals for Sick Children, London. Infants were eligible for inclusion if no major congenital abnormalities were present. For all infants, measurements were made at least three weeks from the onset of any upper respiratory tract infection.

To facilitate comparison between wheezy and healthy infants, they were grouped according to their age at measurement and respiratory status. Group 1 comprised 49 healthy infants aged 13 weeks or less, Group 2, 37 healthy infants aged over 13 weeks and Group 3, 49 infants with physician diagnosed wheeze aged over 13 weeks. Twenty eight of the infants included in Group 1 were studied on a second occasion when more than 13 weeks of age and on the second occasion they were included in Group 2 or 3 according to their respiratory status.

Group 1 infants were aged from 5.0 to 12.6 weeks and weighed from 3.8 to 6.7 kg at testing, Group 2 infants from 17.7 to 61.7 weeks, and from 6.1 to 12.7 kg and Group 3 infants from 15.1 to 74.3 weeks and 3.6 to 13.8 kg. There were 5 Asian infants, 4 Afro-Caribbean infants and 1 infant of mixed ethnic origin in Group 3, the remainder being Caucasian. Although all infants in Group 1 and 2 should have been Caucasian, according to the inclusion criteria for the epidemiological study, 2 of mixed ethnic origin were inadvertently recruited.

4.4.2.2 Measurement protocol

The infants were sedated using triclofos sodium 75 mg·kg⁻¹ (up to 8 weeks) or 100 mg·kg⁻¹ (older infants). Once asleep, the infant was placed within the plethysmograph and airway resistance ($R_{aw}$) measured as described in Section 3.3.2. Measurement of respiratory system resistance ($R_n$) by the SBT and compliance ($C_n$), by both the SBT and multiple occlusion technique (MOT), were then attempted, using the same occlusion shutter, with the infant breathing air as detailed in Section 3.2.4. When possible, occlusions were also performed while the infant was rebreathing warmed, humidified, oxygen enriched air to obtain SBT measurements of $R_m$ under the same conditions as $R_{aw}$. 

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4.4.2.3 Data analysis
All data were analysed as described in Sections 3.3.2 and 3.2.3.3. $R_{sw}$ was calculated from the beginning and end of both inspiration and expiration, i.e. at 4 points throughout the respiratory cycle, giving initial and end inspiratory and expiratory $R_{sw}$, at a flow equivalent ($\pm 20 \text{ mL.s}^{-1}$) to the mean flow recorded during the calculation of $R_n$ by the SBT in each infant.

4.4.2.4 Statistical methods
Unpaired t-tests and a two sample test for proportions were used to compare baseline characteristics and lung function parameters between groups. Comparisons of lung function parameters, obtained by different techniques or under different conditions, were made using the method of Bland and Altman.\(^{133}\)

4.4.3 Results
Technically satisfactory results for both $R_{sw}$ and $R_n$ were obtained on 107 of 135 occasions. As summarised in Table 4.4.1, a significantly higher percentage of $R_n$ measurements failed relative to plethysmographic measurements of $R_{sw}$ (weighted mean from all occasions 19% and 2% respectively; 95% confidence intervals (CI) of the difference $R_n - R_{sw}$: 7%, 27%). This difference was particularly marked in infants over three months of age (i.e. Groups 2 and 3). However, there was no significant difference in the percentage of failed SBT measurements between infants with physician diagnosed wheeze (Group 3) and healthy infants of a comparable age (Group 2) (95% CI for the difference Group 3 - 2: -15%, 20%).

Table 4.4.1: Percentage of occasions when measurements of airway and respiratory resistance were unsuccessful

<table>
<thead>
<tr>
<th>Group 1 Healthy ≤13 weeks</th>
<th>Group 2 Healthy &gt;13 weeks</th>
<th>Group 3 Prior wheeze &gt;13 weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>Failed $R_n$ (%)</td>
<td>12</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Failed $R_{sw}$ (%)</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Both successful (%)</td>
<td>86</td>
<td>78</td>
<td>74</td>
</tr>
</tbody>
</table>

† Weighted mean from all occasions
The main reasons for failure to obtain satisfactory estimates of $R_n$ using the SBT were alinearity of the flow volume curve and failure to equilibrate or achieve a relaxed plateau during airway occlusion which accounted for 54% and 23% of the failures respectively. Other failures were due to early inspiratory effort post occlusion, leaks during the occlusion or a lack of quiet sleep. Successful measurements of $R_{aw}$ were obtained in all but 3 infants, 2 of whom woke before measurements could be completed, and in one of whom severe weather conditions precluded reliable plethysmographic data collection.

Therefore, comparison of $R_n$ and $R_{aw}$ was possible on 107 of 135 occasions (79%) on which paired measurements were attempted. Details of the infants at the time of testing in whom satisfactory paired measurements were obtained are summarised in Table 4.4.2. Of the 42 infants in Group 1, 21 and 7 were included in Groups 2 and 3 respectively when subsequently measured at more than 13 weeks of age. Groups 2 and 3 were, however, independent. Of the 36 infants with prior wheeze, 11 were born at or below 36 weeks gestation and 2 required supplemental oxygen. However only 10 were symptomatic at time of testing.

There were no significant differences between those successfully studied and those in whom one or more measurements failed with respect to sex, body size or specific conductance ($sG_{aw}$) ($p>0.10$ for all parameters). For older infants with successful measurements of $R_n$ and $R_{aw}$, weight and length at time of testing were similar between healthy and wheezy infants ($p>0.10$) (Table 4.4.2).

Table 4.4.2: Details of infants in whom satisfactory measurements of both airway and respiratory resistance were obtained

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Healthy ≤13 weeks</th>
<th>Group 2 Healthy &gt;13 weeks</th>
<th>Group 3 Prior wheeze &gt;13 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>42</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Age mean (SD) (weeks)</td>
<td>8.2 (1.2)</td>
<td>49.8 (10.5)</td>
<td>48.2 (15.0)</td>
</tr>
<tr>
<td>Weight mean (SD) (kg)</td>
<td>5.1 (0.7)</td>
<td>9.5 (1.7)</td>
<td>9.4 (2.0)</td>
</tr>
<tr>
<td>Length mean (SD) (cm)</td>
<td>58.3 (2.4)</td>
<td>75.8 (5.7)</td>
<td>73.4 (6.8)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55</td>
<td>52</td>
<td>61</td>
</tr>
</tbody>
</table>
### Table 4.4.3: Lung function results; mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Healthy ≤13 weeks</th>
<th>Group 2 Healthy &gt;13 weeks</th>
<th>Group 3 Prior wheeze &gt;13 weeks</th>
<th>Group (3 – 2) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRC&lt;sub&gt;pL&lt;/sub&gt; (mL)</td>
<td>142.1 (27.7)</td>
<td>265.3 (51.4)</td>
<td>278.4 (76.1)</td>
<td>-19.0, 44.9</td>
</tr>
<tr>
<td>R&lt;sub&gt;sw&lt;/sub&gt; (kPa·L&lt;sup&gt;−1&lt;/sup&gt;·s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial inspiration</td>
<td>3.4 (1.1)</td>
<td>2.1 (0.9)</td>
<td>2.8 (1.5)</td>
<td>0.1, 1.4*</td>
</tr>
<tr>
<td>End inspiration</td>
<td>2.4 (1.3)</td>
<td>1.5 (0.6)</td>
<td>2.0 (1.3)</td>
<td>0.0, 0.9</td>
</tr>
<tr>
<td>Initial expiration</td>
<td>3.2 (1.4)</td>
<td>2.0 (0.8)</td>
<td>2.3 (0.9)</td>
<td>-0.1, 0.7</td>
</tr>
<tr>
<td>End expiration</td>
<td>4.5 (1.7)</td>
<td>2.7 (1.0)</td>
<td>3.9 (1.7)</td>
<td>0.5, 1.9*</td>
</tr>
<tr>
<td>R&lt;sub&gt;n&lt;/sub&gt; (kPa·L&lt;sup&gt;−1&lt;/sup&gt;·s)</td>
<td>5.3 (1.7)</td>
<td>3.3 (1.0)</td>
<td>4.2 (1.7)</td>
<td>0.3, 1.6*</td>
</tr>
<tr>
<td>C&lt;sub&gt;n,SBT&lt;/sub&gt; (mL·kPa&lt;sup&gt;−1&lt;/sup&gt;·kg&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>12.7 (2.3)</td>
<td>15.4 (2.7)</td>
<td>12.1 (2.5)</td>
<td>-4.6, -2.1***</td>
</tr>
<tr>
<td>C&lt;sub&gt;n,MOT&lt;/sub&gt; (mL·kPa&lt;sup&gt;−1&lt;/sup&gt;·kg&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>13.4 (2.0)</td>
<td>14.4 (2.5)</td>
<td>13.0 (2.4)</td>
<td>-2.6, -0.3***</td>
</tr>
</tbody>
</table>

* = p <0.05, *** = p <0.001

Results from the lung function measurements are summarised in Table 4.4.3. In Group 1, mean (SD) FRC<sub>pL</sub> was 27.9 (5.0) mL·kg<sup>−1</sup> and mean (SD) R<sub>n</sub> 5.3 (1.7) kPa·L<sup>−1</sup>·s while R<sub>sw</sub> ranged from 2.4 to 4.5 kPa·L<sup>−1</sup>·s throughout the respiratory cycle. Amongst the older infants there was a tendency for mean (SD) FRC<sub>pL</sub> per kg to be higher in wheezy compared to healthy infants (29.9 (6.6) and 28.2 (4.1) mL·kg<sup>−1</sup> respectively) but this was not statistically significant (95% CI of the difference Group 3 – 2 : -1.1, 4.3 mL·kg<sup>−1</sup>; p>0.10). Both R<sub>n</sub> and R<sub>sw</sub>, calculated at either initial inspiration or end expiration, were significantly higher amongst wheezy infants than healthy infants of a similar age. However these differences were not significant when R<sub>sw</sub> was calculated at higher lung volumes, i.e. during end inspiration and initial expiration.

There were small but statistically significant differences between C<sub>n</sub> calculated by the MOT and SBT in all three groups (Table 4.4.3). Mean difference (95% CI) was 0.7 (0.2, 1.2) mL·kPa<sup>−1</sup>·kg<sup>−1</sup> (p<0.01) for Group 1, -1.0 (-1.7, -0.4) mL·kPa<sup>−1</sup>·kg<sup>−1</sup>
(p<0.002) for Group 2 and 0.9 (0.3, 1.5) mL·kPa⁻¹·kg⁻¹ (p<0.01) for Group 3. The mean intercept ([MOT + SBT]/2) was approximately 3 mL·kg⁻¹ for all 3 groups of infants. However, while it was slightly higher during the MOT for Groups 1 and 3 (0.6 and 0.9 mL·kg⁻¹ respectively), for Group 2 infants it was, on average, 0.8 mL·kg⁻¹ higher during the SBT.

The relationship between and calculated at matched flows during initial and end expiration for the three Groups of infants (according to the method of Bland and Altman) is shown in Figure 4.4.1, with limits of agreement shown in Table 4.4.4. Despite the wide scatter of results, $R_n$ was significantly (p<0.001) higher than initial expiratory $R_{aw}$ in all three groups of infants. $R_n$ exceeded initial expiratory $R_{aw}$ in all but 2 healthy older infants, and 3 younger healthy infants. Although the differences were smaller, mean $R_n$ was also significantly (p<0.05) higher than $R_{aw}$ calculated at end expiration in Groups 1 and 2. However, there was no significant difference between the two techniques in Group 3 infants (p=0.10). End expiratory $R_{aw}$ exceeded $R_n$ in 28% of infants in both Groups 1 and 2, and in 22% of infants in Group 3.

During measurements of $R_{aw}$ the infant breathed from a bag containing warmed, humidified, oxygen enriched air. This was accompanied by statistically significant increases in respiratory rate (Groups 2 and 3 only), tidal volume and peak tidal expiratory flow (PTEF) (Table 4.4.5). At any given lung volume, flows recorded following release of airway occlusions for the SBT were also significantly higher than those during tidal breathing (data not shown). When approximately 40% of tidal volume had been expired, the point at which analysis of the linear portion of the flow-volume curve usually commenced, flows were approximately 30% higher than the PTEF recorded in that infant during tidal breathing (ranging from 30% less to 115% greater). The mean flow recorded for each infant during the calculation of $R_n$, which was used to denote the point of analysis for $R_{aw}$, was equivalent to 72% (SD 13%) of PTEF during $R_{aw}$ measurements, a similar mean and range of percentages being obtained from all three groups of infants.
Table 4.4.4: Comparison of respiratory and expiratory airway resistance

<table>
<thead>
<tr>
<th></th>
<th>Difference mean (SD)</th>
<th>95% CI</th>
<th>95% limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R_n - R_{aw}$ (initial expiration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy ≤ 13 weeks</td>
<td>1.98 (1.56)</td>
<td>1.51, 2.48***</td>
<td>-1.12, 5.12</td>
</tr>
<tr>
<td>Healthy &gt; 13 weeks</td>
<td>1.29 (0.87)</td>
<td>0.96, 1.62 ***</td>
<td>-0.45, 3.03</td>
</tr>
<tr>
<td>Prior wheeze &gt; 13 weeks</td>
<td>1.97 (1.22)</td>
<td>1.56, 2.38 ***</td>
<td>-0.47, 4.41</td>
</tr>
<tr>
<td>$R_n - R_{aw}$ (end expiration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy ≤ 13 weeks</td>
<td>0.68 (1.86)</td>
<td>0.11, 1.26*</td>
<td>-3.03, 4.40</td>
</tr>
<tr>
<td>Healthy &gt; 13 weeks</td>
<td>0.55 (0.96)</td>
<td>0.19, 0.92*</td>
<td>-1.37, 2.47</td>
</tr>
<tr>
<td>Prior wheeze &gt; 13 weeks</td>
<td>0.31 (1.11)</td>
<td>-0.06, 0.69</td>
<td>-1.91, 2.54</td>
</tr>
</tbody>
</table>

All values as kPa·L⁻¹·s, * = p < 0.05, *** = p < 0.001

Table 4.4.5: Effect of rebreathing on tidal breathing parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline (A)</th>
<th>Rebreathing (B)</th>
<th>95% CI (B - A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy ≤ 13 weeks (n=42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f_a$ (min⁻¹)</td>
<td>45.6</td>
<td>46.6</td>
<td>-0.9, 2.8</td>
</tr>
<tr>
<td>$V_t$ (mL)</td>
<td>42.7</td>
<td>49.6</td>
<td>4.6, 9.2***</td>
</tr>
<tr>
<td>PTEF (mL·s⁻¹)</td>
<td>88.3</td>
<td>98.9</td>
<td>4.1, 16.9*</td>
</tr>
<tr>
<td>Healthy &gt; 13 weeks (n=29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f_a$ (min⁻¹)</td>
<td>29.7</td>
<td>32.9</td>
<td>1.6, 4.7***</td>
</tr>
<tr>
<td>$V_t$ (mL)</td>
<td>106.6</td>
<td>138.5</td>
<td>23.6, 40.4***</td>
</tr>
<tr>
<td>PTEF (mL·s⁻¹)</td>
<td>137.4</td>
<td>182.6</td>
<td>31.5, 58.9***</td>
</tr>
<tr>
<td>Prior wheeze &gt; 13 weeks  (n=36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f_a$ (min⁻¹)</td>
<td>32.7</td>
<td>36.5</td>
<td>2.6, 4.8***</td>
</tr>
<tr>
<td>$V_t$ (mL)</td>
<td>93.7</td>
<td>114.5</td>
<td>12.5, 28.9***</td>
</tr>
<tr>
<td>PTEF (mL·s⁻¹)</td>
<td>138.0</td>
<td>173.3</td>
<td>24.6, 46.1***</td>
</tr>
</tbody>
</table>

Baseline: parameters measured with infant breathing room air. Rebreathing: parameters measured with infant rebreathing warmed, humidified oxygen-enriched air. * = p < 0.05, *** = p < 0.001
Figure 4.4.1: The relationship between respiratory resistance and initial and end expiratory airway resistance

The difference between respiratory resistance ($R_s$) and airway resistance ($R_{aw}$) is plotted against the mean of the two measures of resistance. In plot a) initial expiratory resistance is used and in plot b) end expiratory resistance is used.
Figure 4.4.2: The effect of rebreathing on a) respiratory compliance and b) respiratory resistance assessed by the single breath technique.

- **a)** Respiratory compliance ($C_{rs}$) vs. rebreathing compliance ($C_{rs}$ (rebreathing))
  - Group 1: Healthy infants ≤ 13 weeks of age
  - Group 3: Infants > 13 weeks of age with prior wheeze who were asymptomatic at the time of testing

- **b)** Respiratory resistance ($R_{rs}$) vs. rebreathing resistance ($R_{rs}$ (rebreathing))
  - Group 2: Healthy infants > 13 weeks of age
  - Group 3: Infants > 13 weeks of age with prior wheeze who were symptomatic at the time of testing

Graphs show a linear relationship between $C_{rs}$ and $R_{rs}$ and their respective rebreathing counterparts, with data points grouped according to age and wheeze status.
Table 4.4.6: Effect of rebreathing on respiratory compliance and resistance assessed by the single breath technique

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline (A)</th>
<th>Rebreathing (B)</th>
<th>95% CI (B - A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_n ) (mL·kPa(^{-1}))</td>
<td>18</td>
<td>108.2</td>
<td>128.1</td>
<td>11.5, 28.3 ***</td>
</tr>
<tr>
<td>( R_n ) (kPa·L(^{-1})·s)</td>
<td>18</td>
<td>4.20</td>
<td>3.30</td>
<td>-1.45, -0.33 *</td>
</tr>
<tr>
<td>Intercepts (mL)</td>
<td>18</td>
<td>19.3</td>
<td>31.2</td>
<td>4.7, 19.0 *</td>
</tr>
</tbody>
</table>

\* \( p = < 0.05 \), *** \( p = < 0.001 \)

Repeat measurements of \( C_n \) and \( R_n \) by the SBT while breathing warmed humidified air, as for the \( R_n \) measurements, were achieved in 18 infants (mean (SD) weight 8.3 (2.5) kg, age range 8-61 weeks). There was a significant increase in \( C_n \) during rebreathing, the mean increase (95% CI) being 19.9 (11.5, 28.3) mL·kPa\(^{-1}\). This was accompanied by a significant reduction in \( R_n \). The mean (95% CI) change in \( R_n \) being -0.89 (-1.45, -0.33) kPa·L\(^{-1}\)·s (Table 4.4.6, Figure 4.4.2). There was also a tendency for the volume intercept to increase significantly during rebreathing, both in absolute terms and when corrected for body weight (mean increase (95% CI): 1.2 (0.4, 2.0) mL·kg\(^{-1}\)).

4.4.4 Discussion

The results from this study indicate that, despite the apparent simplicity of the SBT for measuring \( R_n \), the failure rate is higher than that encountered during plethysmographic measurements of \( R_n \) in the same infants. Although the SBT was always attempted after plethysmography, infants were only included in the comparison if reasonable measurement conditions were obtained. It is therefore unlikely that this finding is explained by the SBT measurements being attempted second. The failure rate for the SBT in the current study was considerably lower than that previously reported in preterm infants.\(^{158}\) This probably reflects fewer exclusions due to distortion of the flow-volume curve by excessive modulation of expiratory flow, which was noted in preterm neonates. Nevertheless, the SBT failed on 19% of occasions usually due to alinearity of the flow-volume curve or failure to achieve an adequate plateau. Although the SBT did fail in 2 of the infants with the highest \( R_n \).
values, there was no apparent relationship between failure rate and either symptoms or $R_{sw}$ values. This may reflect the fact that less than one third of the infants studied were symptomatic at testing.

Despite the fact that most of the infants were asymptomatic at time of testing, both $R_n$ and end expiratory $R_{sw}$ were significantly higher amongst infants with prior wheeze than healthy infants of similar age. However, an extremely variable relationship between $R_n$ and $R_{sw}$ was observed within infants. Partitioning of airway resistance from that contributed by the visco-elastic properties of the lung and chest wall is extremely complex. The degree of variability between techniques observed in this study can largely be explained by the numerous factors known to influence the assessment of resistance.

4.4.4.1 Flow and volume dependency of resistance

Airway resistance is known to be both flow and volume dependent, values tending to increase due to turbulence at higher flows, and decrease due to increased elastic recoil and hence distension of the small airways at higher volumes. In addition, at any given lung volume or flow, $R_{sw}$ is generally lower during inspiration than expiration due to the distending influence of the negative inspiratory intrapleural pressure on intrathoracic structures. In adults and healthy infants, in whom the chest wall has begun to stiffen, such changes may be fairly minimal over the tidal range so that stable values of $R_{sw}$ are achieved. However, the highly compliant chest wall of young infants results in a low transpulmonary pressure at end expiration, such that dynamic airway closure with marked elevation of end expiratory resistance can occur within the tidal range. This tendency may be more pronounced in infants with airway disease due to an increased pressure gradient along the airways in the presence of airway obstruction and/or the rise in intrapleural pressure which will accompany any active expiratory efforts. In adults, the stiffness of the bronchial wall protects the conducting airways from deformation and collapse due to positive intrathoracic pressures that develop during forced expiratory efforts. However, airways from immature animals are far more compliant than those in adults and hence vulnerable to collapse at smaller transmural pressures. Consequently changes in lung volume
which alter the interdependence between airways and parenchyma may act as a major determinant of airway calibre and resistance in infants. In this study, changes in $R_{sw}$ were found to occur throughout the respiratory cycle in all three groups of infants (Table 4.4.3).

Attempts were made to minimise potential sources of variability when making comparisons between techniques by analysing $R_n$ and $R_{sw}$ at similar flows and phases of respiration. Since $R_n$ is measured during passive expiration following an end inspiratory occlusion, it may reflect the mechanics of the airways during initial expiration (together with a chest wall and tissue component) most closely.\(^{164}\) However, since analysis is performed on the descending portion of the flow-volume curve after peak expiratory flow has been attained, it could also reflect airway characteristics towards end expiration. Consequently $R_n$ was compared with both initial and end expiratory $R_{sw}$. $R_{sw}$ was calculated at the average flow recorded during $R_n$ analysis in each infant which proved to be approximately 72% of PTEF, i.e. similar to $R_{sw}$ at two-thirds PTEF, which has been conventionally calculated in the past.\(^{142,165}\) However, these attempts to match flows can at best only be an approximation, with slight discrepancies being potentially responsible for much of the observed variability.

**4.4.4.2 Potential influence of the rebreathing bag**

Even when attempting to match flows and phase of respiration, we could not control for the potential changes in resistance induced by rebreathing warm humidified air. Adults are conventionally requested to pant during plethysmographic assessments of $R_{sw}$; both to minimise pressure changes due to alterations in temperature and humidity of respired gas and to keep the glottis wide open, thereby minimising upper airway resistance. Since infants cannot be asked to pant, they are allowed to rebreathe warm humidified air but this will inevitably result in some build up of carbon dioxide and thereby increase ventilatory drive (Table 4.4.5). This effect was less marked in the youngest infants (Group 1), reflecting their smaller minute ventilation in relation to the volume within the rebreathing bag.
It is not clear from the current study whether the reduction in $R_n$ which occurred when measurements were repeated during rebreathing (Figure 4.4.2b, Table 4.4.6) reflect a bronchodilator effect of carbon dioxide per se, increased tidal volume or increased dynamic elevation of lung volume subsequent to the increase in minute ventilation (i.e. volume dependence of $R$). The accompanying rise in $C_n$ and volume intercept during rebreathing (Table 4.4.6) suggests that a change in lung volume may be a contributory factor. If so, this has important implications with respect to timing of lung volume measurements during plethysmography.

### 4.4.4.3 Influence of changes in gas composition

During this study the pneumotachograph was calibrated with air which may have introduced a slight error into measurements during the rebreathing of oxygen enriched air ($F_{1O_2} \approx 0.40$). However, such errors are likely to be small and would not account for the differences reported in Table 4.4.4. Theoretically, $C_n$ could be overestimated and $R_n$ underestimated by 11% if an infant breathed 100% oxygen through a pneumotachograph calibrated in air, due to the relatively high viscosity of oxygen compared with air. However, this error falls to 2% at an $F_{1O_2}$ of 0.4, and would be further compensated by an increase in $F_{1CO_2}$ in the bag during rebreathing, since the viscosity of carbon dioxide is lower than that of air.

It was not feasible to measure $R_n$ under identical conditions to $R_{aw}$ in all infants, nor to repeat the MOT assessment of $C_n$ during rebreathing, since this part of the study was only attempted if infants remained asleep at the end of the main measurement protocol. Furthermore, many infants failed to relax adequately under conditions of stimulated breathing. Nevertheless the observations in the subgroup of 18 infants emphasise the marked influence of measurement conditions on measured values of respiratory function and hence variability between techniques.

### 4.4.4.4 Partitioning of respiratory system resistance

Previous studies in which pulmonary and airway resistance have been measured simultaneously and analysed at identical flows suggest that lung tissue resistance makes a relatively small (<15%) contribution to total pulmonary resistance. This
may be related to the fact that the major component of lung tissue resistance is thought to be due to hysteresis of the lung which, since it is inversely proportional to breathing frequency, will make a smaller contribution in rapidly breathing infants than adults.

The contribution of the chest wall is more controversial, since differences between techniques often preclude direct comparison. Theoretically $C_n$ and $R_n$ can be partitioned into lung, airway and chest wall components by measuring the relevant driving pressure. However, under normal functional conditions the driving pressure across the chest wall is a combination of static elastic properties and the pressure generated by activity of the chest wall muscles. Accordingly, the passive mechanical properties of the chest wall can only be derived when muscle activity is inhibited. In a comparative study of pulmonary and total respiratory resistance, Gerhardt et al found that $R_n$ was approximately 24% higher than pulmonary resistance ($p<0.001$) in infants at approximately 1 year of age. However, no significant difference was observed in preterm neonates, a finding which was attributed to the highly compliant chest wall in immature infants.

Within individuals in this study, $R_n$ was, on average, 80% greater than $R_{aw}$ during initial expiration and 27% greater than $R_{aw}$ during end expiration in both groups of healthy infants, these values being 100% and 15% respectively among the wheezy infants. However, there was huge individual variability and it is not meaningful to calculate a value for tissue resistance or visco-elasticity simply as the difference between the two techniques.

### 4.4.4.5 Passive versus dynamic resistance

In addition to differences in measurement conditions discussed above, $R_n$ assesses expiratory resistance under passive conditions, whereas $R_{aw}$ reflects the dynamic changes that occur during tidal breathing. Despite obvious alinearities of the pressure-flow loop during $R_{aw}$ measurements, a linear flow-volume relationship was frequently obtained from infants with airway disease (Figure 4.4.3). Indeed the failure rate of the SBT due to alinearity was no greater amongst the group with prior wheeze than in healthy infants of a similar age. Following end inspiratory occlusions, infants
Figure 4.4.3: a) An apparently linear flow-volume curve obtained with the SBT. b) Example of a pressure-flow curve obtained in the same infant showing elevated end expiratory airway resistance.
frequently inspire earlier than usual on the subsequent breath, such that any rise in end expiratory resistance due to dynamic airway closure may be missed. Furthermore, analysis of the “passive” time constant is limited to the “linear” portion of the flow volume curve, when any muscle activity has supposedly been inhibited. Consequently measurements of $R_n$ may reflect the dimensions of the airways under passive conditions, but cannot reflect the dynamic changes which normally occur throughout the breath. This would explain why values of end expiratory $R_{sw}$ exceeded those of $R_n$ in approximately 25% of infants studied.

Similar findings were recently reported by Springer et al.\textsuperscript{164} This group found virtually identical values of weight corrected FRC$_{plut}$ in 15 “normal” and 9 post-bronchiolitic infants as in the current Group 2 and 3 (healthy $>$13 weeks and prior wheeze respectively). Springer et al did not tabulate absolute values of $R_n$ and $R_{sw}$, making direct comparisons difficult, but their published illustrations reveal that initial expiratory $R_{sw}$ was equal to or exceeded $R_n$ in approximately one third of the mixed population and that end expiratory $R_{sw}$ was significantly greater than $R_n$ amongst the wheezy infants, many of whom were symptomatic at time of testing.

During the SBT, time is allowed during the end inspiratory occlusion for relaxation of the diaphragm and other inspiratory muscles. It could therefore be argued that the level of activity of the inspiratory and laryngeal expiratory muscles during analysis of the passive flow volume curve most closely resembles that occurring at mid-expiration during tidal breathing and that $R_n$ should therefore be compared to mid-expiratory $R_{sw}$. However, the higher flows occurring towards mid-expiration were associated with increased values for $R_{sw}$, presumably due to increased turbulence\textsuperscript{165} and this approach would therefore tend to increase rather than diminish any discrepancies between $R_{sw}$ and $R_n$.

4.4.4.6 Validity of the SBT

Concern has been expressed regarding the use of the SBT in unintubated infants due to possible laryngeal modulation of expiratory air flow resulting in a falsely elevated volume intercept and hence $C_n$ and $R_n$.\textsuperscript{102,158,171} In addition, a linear shape on the flow-volume curve does not necessarily indicate relaxation of respiratory muscles or
the presence of a single time constant, since an even, descending slope could represent balanced respiratory muscle activity and/or reciprocal changes in compliance and resistance as lung volume decreases. \( C_n \) was measured using both the MOT and SBT in an attempt to validate measurements of \( R_n \) with respect to these potential problems and small differences were found between the two techniques, which appeared to be primarily attributable to small variations in the size of the volume intercept. Nevertheless, it should be noted that although the differences between techniques were statistically significant, the magnitude of these differences is probably too small to be of physiological significance or to influence results markedly.

### 4.4.5 Conclusions

Despite the difficulties in interpreting results from individual infants and the relatively high failure rate, the SBT was simple to use and is potentially far more applicable than plethysmography, which is essentially limited to specialised laboratories and generally unsuitable for critically ill infants. Although it has been suggested that \( R_n \) may reflect initial expiratory airway mechanics, this is still open to debate. In this study both \( R_n \) and end expiratory \( R_{en} \) were significantly higher in infants with prior wheeze, most of whom were asymptomatic at time of testing, than in healthy infants of similar age and weight. This suggests that measurements of \( R_n \) may be of value in epidemiological studies. However, further work is needed to define the extent to which elevated values of \( R_n \) correctly identify those infants with airflow obstruction, as determined by clinical symptoms or other objective measures of airway function. Furthermore, the clinical value of measurements of \( R_n \) within individual infants may be limited by its failure to detect the dynamic changes in resistance throughout the breath that are clearly evident during plethysmographic studies.
4.5 Respiratory morbidity and respiratory function in the first year of life following repair of oesophageal atresia

4.5.1 Introduction and aims

Oesophageal atresia with distal tracheo-oesophageal fistula is a common congenital anomaly with an incidence of 1 in 3500.\(^{172}\) Successful repair by direct anastomosis was first described in the 1940s.\(^{173}\) Initially the mortality was high particularly for low birth weight infants, those with pneumonia and those with other congenital anomalies.\(^{174}\) In recent years survival has been approximately 90% even in these high risk infants, and approaches 100% in babies with no other problems.\(^{172}\) With the improvement in mortality, increasing attention is being focused on morbidity and long term outcome particularly respiratory complications and lung function.

Despite technically satisfactory repair, these children frequently have persistent cough and an increased incidence of lower respiratory tract infections, especially in the first few years of life.\(^ {175}\) However there have been few studies of respiratory function in the survivors of oesophageal atresia. Those that had been published prior to the inception of this thesis have involved older children and adults\(^{176-179}\) (Table 4.5.1). In all the studies the history of early symptoms has been obtained retrospectively, based on parental recall and review of medical notes.

The aims of this study were to:

- determine respiratory function at the age of one year
- prospectively document the prevalence of respiratory symptoms in the first year of life after surgical correction of oesophageal atresia
- assess the feasibility of respiratory function measurements in early infancy, using tidal breathing parameters and occlusion techniques during natural sleep

4.5.2 Subjects and methods

Infants with surgically treated oesophageal atresia and tracheo-oesophageal fistula were recruited to the study from the surgical wards of The Hospital for Sick Children, Great Ormond Street over a two year period from March 1993-1995. Infants diagnosed as having congenital heart disease requiring surgery in the first year of life
Table 4.5.1: Respiratory function in patients with repaired oesophageal atresia

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Age (years)</th>
<th>Respiratory function tests</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milligan et al 1979</td>
<td>24</td>
<td>7-18</td>
<td>plethysmography spirometry methacholine challenge</td>
<td>1 normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 obstructive disease (8 +ve methacholine challenge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 restrictive disease (2 +ve methacholine challenge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 +ve methacholine challenge only</td>
</tr>
<tr>
<td>Couriel et al 1982</td>
<td>20</td>
<td>8-17</td>
<td>plethysmography spirometry histamine challenge</td>
<td>compared to a control group, recruited for an epidemiological study, a modest restrictive defect was present. 22 % +ve histamine challenge</td>
</tr>
<tr>
<td>Le Souëf et al 1987</td>
<td>18</td>
<td>12-21</td>
<td>plethysmography spirometry oesophageal function</td>
<td>normal lung function in those with no history of early childhood pneumonia, modest restrictive defect in those with early childhood pneumonia</td>
</tr>
<tr>
<td>Chetcuti et al 1989</td>
<td>154</td>
<td>over 6</td>
<td>plethysmography spirometry (lung volumes only)</td>
<td>patients with scoliosis but not with anterior chest wall deformity alone had mild restrictive defects</td>
</tr>
</tbody>
</table>
or other major congenital anomalies were excluded. Infants of families without a good command of written and spoken English were also excluded.

Respiratory symptoms during the first year of life were documented prospectively by the parents using daily diary cards (Appendix 1). Data collection commenced when the infants were discharged from hospital and continued until the first birthday or the one year lung function assessment, which ever occurred later. Completed cards were collected from parents when attending the surgical outpatient clinic. Additional information was obtained from the outpatient follow-up notes especially in infants who withdrew from the study. Respiratory function tests were performed at one year of age when the infants were free of acute respiratory tract infection. FRC and airway resistance were measured using whole body plethysmography. Total respiratory compliance was measured using the multiple occlusion technique. Airway function was further assessed in some subjects using the rapid thoraco-abdominal compression technique (RTC), which became available in the laboratory part way through the research period. All measurements were made during quiet sleep after sedation with oral triclofos sodium (100 mg·kg⁻¹). The apparatus dead space was 26 mL and resistance 0.48 kPa·L⁻¹·s (at 100 mL·s⁻¹) for plethysmography and compliance measurements. The dead space was 10 mL and resistance 0.10 kPa·L⁻¹·s (at 100 mL·s⁻¹) for the RTC. Full details of the equipment and measurement methods are given in Sections 3.3.2 (plethysmography), 3.2.4 (passive mechanics), and 3.4.2 (RTC).

To assess the feasibility of respiratory function measurements in early infancy using tidal breathing parameters and occlusion techniques during natural sleep, measurements were attempted on the wards prior to discharge from the hospital (either to home or the referring neonatal unit). Further measurements were attempted in the respiratory laboratory when the infants were attending the hospital for surgical outpatient clinics. Although the age at follow up appointments varied, most infants made two visits during the first six months of life.

Prior to discharge from hospital the following measurement protocol was attempted. Infants were measured lightly clothed in a loose vest or body suit. A period of tidal
breathing, sufficient to allow analysis of at least 30 breaths, was recorded using respiratory inductance plethysmography (RIP). A face mask connected to a pneumotachograph (PNT) was then positioned over the infant’s mouth and nose and a further period of tidal breathing recorded to permit analysis of simultaneous RIP signals and PNT flow and volume signals. The RIP bands were then unfastened and data collected for analysis of at least 30 breaths of tidal breathing through the face mask and PNT alone. A series of brief airway occlusions was then made to permit determination of total respiratory compliance by the multiple occlusion technique, and determination of total respiratory compliance and resistance by the single breath technique. Apparatus dead space was kept to less than 2 mL·kg⁻¹ by manually occluding the PNT rather than using a mechanical shutter in the smallest infants. Full details of the measurement methods are given in Sections 3.5.2 (RIP), 3.1.3 (tidal breathing parameters) and 3.2.4 (passive mechanics). Only data collected during behaviourally determined quiet sleep were accepted. In practice the measurement protocol was often interrupted by the infant waking. A similar protocol was applied in the respiratory laboratory during outpatient visits except that measurements using the occlusion techniques were usually attempted prior to RIP data collection.

4.5.3 Results

4.5.3.1 Respiratory morbidity and one year respiratory function
Twenty two infants were recruited to the study. Twenty one infants had oesophageal atresia and distal tracheo-oesophageal fistula managed by primary anastomosis and ligation of the fistula. The remaining infant had a proximal fistula and was managed by ligation of the fistula and gastrostomy in the neonatal period and gastric interposition at 6 months of age. Details of the infants are given in Table 4.5.2. Full diary card data were obtained for 17 infants and one year respiratory function tests were performed in 15 infants. One family was unable to find a satisfactory time for their child to be measured and the other family had moved to Scotland. Of the five infants that were withdrawn before the end of the one year study period, 1 term infant was withdrawn after sustaining hypoxic cerebral damage during a choking episode and one very preterm infant (GA 29 weeks) sustained a cardiac arrest and cerebral damage prior to discharge from the referring neonatal unit. Two other families
changed their minds about participating in the study. One of these infants is known to have had an aortopexy during the first year of life for stridor and the diary card data that were collected for the other infant shows this infant suffered from recurrent coughing and choking. The remaining family withdrew when the infant was 9 months of age as they were moving to Ireland. This infant had only uncomplicated upper respiratory tract infections prior to withdrawal from the study.

The respiratory morbidity data are given in Table 4.5.2. Of the 22 infants recruited to the study only 3 were known to have had no respiratory symptoms other than uncomplicated upper respiratory tract infections (URTIs) during the first year of life. One infant followed for 9 months also had only uncomplicated URTIs. A further 4 infants had URTIs complicated by wheezing or chest infections but were well between their infections. The remaining infants suffered from recurrent wheezing or severe coughing, stridor or significant choking episodes. In 2 infants the choking episodes were life threatening, 1 leading to hypoxic cerebral damage.

The results of respiratory function tests at one year are given in Table 4.5.3. The infants clinical status during the year is indicated. Infants clinical status is classified as 0 if they had only uncomplicated URTIs, 1 if they had wheezing with URTIs or had chest infections and 2 if they had recurrent wheezing or severe coughing, stridor or severe choking episodes. FRC values of 24-36 mL·kg⁻¹ would be expected in healthy one year olds. Only subject no.16, who had severe coughing and wheezing with 2 episodes of bronchiolitis during the first year had a significantly elevated FRC (394 mL, 43.8 mL·kg⁻¹). The respiratory compliance values were within normal limits for all infants measured based on values for healthy 1 year olds obtained in the same laboratory (149.0 ±20.6 mL·kPa⁻¹ (range 10.7-18.5 mL·kPa⁻¹·kg⁻¹). Data were not collected for one infant and the method failed due to a lack of relaxed pressure plateaux in one other infant.

Plethysmographic airway function data are presented as $G_{ow}$, calculated at early inspiratory and end expiratory flows equal to the 50% mean peak inspiratory and expiratory flows respectively, plotted against FRC in Figure 4.5.1.a and b. Plotted on the same Figures are values obtained in the same laboratory for a group of 51 healthy infants age 11-17 months measured as part of an epidemiological study. Only one
### Table 4.5.2: Infant details and one year respiratory morbidity data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>GA (weeks)</th>
<th>BWt (kg)</th>
<th>Respiratory symptoms in 1st year of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infants completing diary cards and one year respiratory function measurements</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>40</td>
<td>3.6</td>
<td>uncomplicated URTIs only</td>
</tr>
<tr>
<td>3*</td>
<td>M</td>
<td>34</td>
<td>1.9</td>
<td>wheezing associated with URTIs</td>
</tr>
<tr>
<td>4*</td>
<td>M</td>
<td>31</td>
<td>1.5</td>
<td>episodes of wheezing with and without URTIs, intermittent stridor</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>31</td>
<td>1.6</td>
<td>episodes of wheezing with and without URTIs</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>36</td>
<td>2.0</td>
<td>recurrent wheezing and stridor especially with feeding, life threatening choking episode</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>40</td>
<td>4.0</td>
<td>recurrent coughing and wheezing, 2 episodes of severe choking</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>33</td>
<td>1.6</td>
<td>severe recurrent coughing</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>40</td>
<td>3.8</td>
<td>uncomplicated URTIs only (aortic coarctation diagnosed and repaired age 6 months)</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>40</td>
<td>2.8</td>
<td>recurrent coughing especially with feeding</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>38</td>
<td>2.3</td>
<td>episodes of wheezing associated with URTIs</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>41</td>
<td>3.5</td>
<td>severe coughing and wheezing, 2 episodes of bronchiolitis</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>41</td>
<td>2.6</td>
<td>1 LRTI</td>
</tr>
</tbody>
</table>
Infants completing diary cards and one year respiratory function measurements continued

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>M</td>
<td>37</td>
<td>3.2 severe coughing, stridor and chest infections, required surgery for recurrent fistula</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>41</td>
<td>3.8 severe coughing, stridor and choking, 1 LRTI</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>40</td>
<td>2.9 2 LRTIs with wheezing</td>
</tr>
</tbody>
</table>

Infants completing diary cards only

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7**</td>
<td>M</td>
<td>37</td>
<td>2.7 recurrent wheezing and LRTIs</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>39</td>
<td>3.1 uncomplicated URTI only</td>
</tr>
</tbody>
</table>

Infants withdrawn from study before completion of diary cards

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>37</td>
<td>2.2 severe choking episode leading to cardiac arrest and cerebral damage (age 4 months) one previous uncomplicated URTI and one other choking episode</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>29</td>
<td>1.2 LRTI leading to cardiac arrest and cerebral damage in early infancy</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>36</td>
<td>2.2 no diary cards, severe stridor requiring aortopexy</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>41</td>
<td>3.0 uncomplicated URTIs only until aged 9 months when went abroad</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>39</td>
<td>3.2 withdrawn age 10 months, recurrent choking and coughing</td>
</tr>
</tbody>
</table>

GA = gestational age, Bwt = birth weight, * = twin, ** = infant managed with gastrostomy and cervical oesphagostomy until gastric interposition aged 6 months, URTI = upper respiratory tract infection, LRTI = lower respiratory tract infection
Table 4.5.3: One year respiratory function data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (m)</th>
<th>Wt (kg)</th>
<th>L (cm)</th>
<th>Status</th>
<th>FRC mean (SD) (mL)</th>
<th>C_{rs} mean (95%CI) (mL·kPa^{-1})</th>
<th>V'_max,FRC mean (SD) (mL·s^{-1})</th>
<th>II sG_{aw} mean (s^{-1}·kPa)</th>
<th>EE sG_{aw} mean (s^{-1}·kPa)</th>
<th>Shape of resistance loops</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>11.9</td>
<td>11.3</td>
<td>82</td>
<td>0</td>
<td>313 (16)</td>
<td>121 (103, 138)</td>
<td>—</td>
<td>2.23</td>
<td>1.73</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>13.1</td>
<td>10.4</td>
<td>78</td>
<td>1</td>
<td>323 (7)</td>
<td>168 (135, 201)</td>
<td>—</td>
<td>1.50</td>
<td>1.11</td>
<td>normal</td>
</tr>
<tr>
<td>4</td>
<td>14.0</td>
<td>11.8</td>
<td>82</td>
<td>2</td>
<td>285 (10)</td>
<td>131 (120, 143)</td>
<td>—</td>
<td>2.78</td>
<td>1.88</td>
<td>normal</td>
</tr>
<tr>
<td>5</td>
<td>11.9</td>
<td>9.7</td>
<td>73</td>
<td>2</td>
<td>233 (6)</td>
<td>105 (91, 120)</td>
<td>—</td>
<td>1.86</td>
<td>0.97</td>
<td>abnormal insp. and exp.</td>
</tr>
<tr>
<td>6</td>
<td>12.6</td>
<td>7.9</td>
<td>75</td>
<td>2</td>
<td>214 (7)</td>
<td>94 (85, 103)</td>
<td>79.4 (6.0)</td>
<td>1.44</td>
<td>0.76</td>
<td>abnormal insp. and exp.</td>
</tr>
<tr>
<td>7</td>
<td>11.7</td>
<td>10.7</td>
<td>78</td>
<td>2</td>
<td>298 (10)</td>
<td>134 (125, 143)</td>
<td>34.2 (2.8)</td>
<td>1.66</td>
<td>1.27</td>
<td>normal</td>
</tr>
<tr>
<td>8</td>
<td>13.0</td>
<td>11.2</td>
<td>77</td>
<td>2</td>
<td>294 (12)</td>
<td>137 (123, 150)</td>
<td>98.5 (4.9)</td>
<td>1.26</td>
<td>1.16</td>
<td>abnormal insp. and exp.</td>
</tr>
<tr>
<td>9</td>
<td>12.1</td>
<td>9.3</td>
<td>75</td>
<td>0</td>
<td>333 (9)</td>
<td>107 (92, 122)</td>
<td>208.0 (3.7)</td>
<td>3.23</td>
<td>2.55</td>
<td>normal</td>
</tr>
<tr>
<td>10</td>
<td>14.0</td>
<td>10.8</td>
<td>82</td>
<td>2</td>
<td>305 (12)</td>
<td>—</td>
<td>90.5 (31.3)</td>
<td>0.80</td>
<td>1.34</td>
<td>abnormal insp. and exp.</td>
</tr>
<tr>
<td></td>
<td>Wt</td>
<td>L</td>
<td>Status</td>
<td>S 1</td>
<td>S 2</td>
<td>S 3</td>
<td>I 1</td>
<td>I 2</td>
<td>I 3</td>
<td>I 4</td>
</tr>
<tr>
<td>---</td>
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<td>----</td>
</tr>
<tr>
<td>15</td>
<td>11.7</td>
<td>8.6</td>
<td>74</td>
<td>1</td>
<td>274 (3)</td>
<td>121 (111, 131)</td>
<td>167.0 (4.5)</td>
<td>2.79</td>
<td>2.36</td>
<td>normal</td>
</tr>
<tr>
<td>16</td>
<td>11.9</td>
<td>9.0</td>
<td>78</td>
<td>2</td>
<td>394 (4)</td>
<td>120 (110, 131)</td>
<td>124.9 (3.3)</td>
<td>1.64</td>
<td>1.79</td>
<td>abnormal insp.</td>
</tr>
<tr>
<td>17</td>
<td>12.1</td>
<td>9.2</td>
<td>79</td>
<td>1</td>
<td>326 (11)</td>
<td>165 (146, 184)</td>
<td>192.5 (21.4)</td>
<td>2.77</td>
<td>2.65</td>
<td>normal</td>
</tr>
<tr>
<td>18</td>
<td>13.4</td>
<td>9.2</td>
<td>77</td>
<td>2</td>
<td>243 (3)</td>
<td>91 (84, 98)</td>
<td>155.1 (16.5)</td>
<td>2.23</td>
<td>1.99</td>
<td>normal</td>
</tr>
<tr>
<td>21</td>
<td>12.8</td>
<td>13.8</td>
<td>79</td>
<td>2</td>
<td>366 (12)</td>
<td>failed</td>
<td>70.2 (5.5)</td>
<td>0.49</td>
<td>0.19</td>
<td>abnormal exp.</td>
</tr>
<tr>
<td>22</td>
<td>11.7</td>
<td>9.2</td>
<td>77</td>
<td>1</td>
<td>252 (11)</td>
<td>105 (85, 126)</td>
<td>151.4 (22.7)</td>
<td>3.20</td>
<td>2.23</td>
<td>normal</td>
</tr>
</tbody>
</table>

Wt = weight at time of test, L = length at time of test, insp. = inspiration, exp. = expiration. Status refers to respiratory symptoms during 1st year of life, 0 = uncomplicated upper respiratory tract infections only, 1 = wheezing with URTIs or lower respiratory tract infections, 2 = chronic symptoms. I sG<sub>in</sub> = specific conductance at initial inspiration, EE sG<sub>ex</sub> = specific conductance at end expiration.
Infants with oesophageal atresia (OA) are coded according to their respiratory status during the first year of life (as in Table 4.5.3). Normal data for healthy infants aged 11-17 months recruited for an epidemiological study.\textsuperscript{131}
Figure 4.5.2: Examples of plethysmographic pressure-flow loops

a) normal loop (Subject no.10), b) abnormal inspiratory pattern (Subject no.16), c) abnormal expiratory pattern (Subject no.21) and d) abnormal inspiratory and expiratory pattern (Subject no.7)

infant, subject no.6 who had severe respiratory symptoms falls below the values found in the healthy controls. However qualitative assessments of the resistance loops for each infant show that 6 of the 15 infants had abnormalities. All these infants had recurrent wheezing or severe coughing, stridor or choking episodes. Examples of abnormal resistance loops are shown in Figure 4.5.2.
The rapid thoraco-abdominal compression technique for the measurement of $V'_{\text{max, FRC}}$ to assess small airway function only became available in the laboratory part way through the study and therefore data are only available for 11 of the infants. The values for the infants with oesophageal atresia have been plotted along with reference data for normal infants aged 10.5-14.5 months provided by Tepper et al\textsuperscript{181} in Figure 4.5.3. This shows that the values of $V'_{\text{max, FRC}}$ in the infants with oesophageal atresia were low and that the greater the respiratory morbidity during the first year the lower the value of $V'_{\text{max, FRC}}$.

**Figure 4.5.3:** $V'_{\text{max, FRC}}$ plotted against length for infants with oesophageal atresia and normal infants

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Infants with oesophageal atresia (OA) are coded according to their respiratory status during the first year of life (as in Table 4.5.3). Normal data for infants aged 11-15 months from Tepper et al.\textsuperscript{181}
4.5.3.2 The feasibility of respiratory function testing during natural sleep

Data from the first 10 subjects recruited, are presented to illustrate the major practical problems and low success rate of unsedated simpler measurements in early infancy. Measurements prior to discharge were attempted at age 7-14 days in all infants. One infant (subject no.2) was studied on the afternoon prior to discharge and in the 90 minutes available only RIP without PNT data were obtained as the infant spent most of the time awake. In the remaining 9 infants, data collection spanned 50-270 minutes in addition to the time taken for the infants to go to sleep. The very extended data collection times relate to the infants waking and large periods of time in non quiet sleep. Most measurements were attempted in the late evening when the ward was quiet and time relatively unlimited. In these infants tidal breathing parameters using a face mask and PNT were always obtained. The multiple occlusion technique for measuring $C_n$ was successful in 8/9 subjects; it failed due to a lack of relaxed pressure plateaux in the remaining subject. The single breath technique was successful in only 4/9 subjects but in these subjects there was good agreement between $C_{n,MOT}$ and $C_{n,SBT}$. In one case the data collection was poor as the occlusions were held too long, however in the other infants there was no pressure plateau at end inspiration (n=4), the expiratory flow volume curve was alinear (n=2) or the infant inspired early during the passive expiration (n=1) (see Figure 4.5.4). Data obtained using RIP alone were adequate to determine respiratory rate in all subjects, but the signals were often of relatively low voltage and yielded a poor differentiated signal. Signals obtained with RIP while the PNT was in simultaneous use were of better quality (Figure 4.5.5). The respiratory patterns observed with RIP while waiting for the infants to go to sleep were so variable that consistent analysis of tidal breathing parameters would have been impossible.

These 10 infants each attended the laboratory on two further occasions in early infancy when visiting the hospital for clinic appointments. The age range of the infants was 5.7-15.3 weeks on the first visit and 18.0-33.6 weeks on the second visit. On two occasions no attempt to make measurements was made, one because the infant was very unsettled with an URTI, and the other because the infant required
Figure 4.5.4: Examples of SBT failures

4.5.4a): Time based trace showing failure to reach a pressure plateau and early inspiration following release of occlusion. 4.5.4b): A flow-volume curve from the same infant demonstrating alinearity. Data from subject no. 2.
Figure 4.5.5: Examples of RIP data

4.5.5a): Data collected during quiet sleep before the application of the face mask and pneumotachograph. 4.5.5b): Data collected 3 minutes later but with the face mask and pneumotachograph in place. The calibration and scales are the same. Note the larger voltage signals and better RIP “flow” signal.

echocardiography to assess a newly diagnosed aortic coarctation. Attempts to obtain measurements in the other infants were usually continued for 2-3 hours depending on the wishes of the parents. 1 infant (subject no.9, age 15 weeks) failed to sleep at all
and 1 infant (subject no.6, age 18 weeks) slept only a few minutes allowing the collection of 10 breaths of tidal breathing only. Therefore some data were available from 16 measurement sessions. On these 16 occasions tidal breathing parameters using a PNT were always obtained. Although the multiple occlusion technique was also tried on all occasions, there were 4 failures due to lack of relaxed pressure plateaux across an adequate range of occluded volumes. On 12 occasions there was time to attempt the SBT which failed in 4 infants due to lack of pressure plateaux at end inspiration, alinearity of the expiratory flow volume curve, or early inspiration. Of the remaining 8 apparently successful measurements, one gave a $C_n$ substantially lower than that obtained with the MOT. Due to time constraints, RIP data was only obtained on 13 occasions.

4.5.4 Discussion

The prospective documentation of respiratory symptoms during the first year of life confirmed that survivors of oesophageal atresia have a high incidence of respiratory problems. Of the 22 infants recruited to the study only 3 reported a year in which the only symptoms had been uncomplicated upper respiratory tract infections (URTIs). One other infant, for whom diary card data were only obtained for 9 months, also had uncomplicated URTIs. A further 3 infants suffered from wheezing associated with respiratory tract infections and 1 infant was well apart from a single chest infection. This history would be common in the general population. The remaining 14 infants had more severe symptoms, with 2 children withdrawn from the study after sustaining cerebral damage secondary to a respiratory problems. One of these infants had been born at 29 weeks gestation, however the other was a term infant.

Lung function measurements in 15 infants at 1 year showed a very high incidence of abnormality mainly of airway function, detected with the rapid thoraco-abdominal compression technique and plethysmography. The relative advantages and disadvantages of the rapid thoraco-abdominal compression technique for the assessment of airway function are discussed in Section 6.2.3. Infants with respiratory symptoms throughout the year were much more likely than the few healthy infants to have abnormal respiratory function. Most previous studies of respiratory function in survivors of oesophageal atresia have involved older children and adults. Both
restrictive defects and abnormalities of airway function have been documented (Table 4.5.1). The only other study to report results in infants was published recently by Beardsmore et al.\textsuperscript{182} They studied 16 infants within 3 months of primary surgery. Eight infants had been clinically well from a respiratory perspective and all but one of these had respiratory function which fell within the normal range. Plethysmographic airway function abnormalities were detected in the remaining 8 infants all of whom had respiratory symptoms. This group found $V'_{\text{max,FRC}}$ measurements were normal in the asymptomatic group. Measurements of $V'_{\text{max,FRC}}$ were only attempted in 5 of their symptomatic infants and failed in 3 of these. $V'_{\text{max,FRC}}$ was within normal limits in the remaining 2 symptomatic infants, although unfortunately full details regarding reference values were not given. In contrast to the study group of Beardsmore et al, the population reported here includes preterm and low birthweight infants although these factors are unlikely to explain the abnormalities in 1 year respiratory function as no infant was diagnosed as having bronchopulmonary dysplasia.

The assessment of respiratory function in this group of infants using tidal breathing parameters and occlusion techniques did not prove feasible in early infancy. Measurements were too time-consuming to be of value in the clinical setting. Although tidal breathing parameters and compliance using the multiple occlusion technique were possible in many infants, the failure rate for the single breath technique was very high. Over recent years the value of tidal breathing parameters in assessing airway function has been increasingly challenged (Section 6.2.1). As the main interest is in abnormalities of airway function, ability to measure total respiratory compliance using the multiple occlusion technique is of limited value. The problems of the passive respiratory mechanics techniques particularly in infants with significant airway pathology are discussed in Section 6.2.2.

4.5.5 Conclusions

A prospective documentation of respiratory symptoms during the first year of life confirms that survivors of oesophageal atresia have a high incidence of respiratory problems. These infants have evidence of respiratory function abnormalities, particularly airway function abnormalities, when measured at 1 year of age. Reliable measurement of passive respiratory mechanics and tidal breathing parameters in early
infancy during natural sleep as a method of assessing these infants proved impracticable.
5. Respiratory function measurements during assisted ventilation

A series of studies into the measurement of respiratory function in infants receiving respiratory support is presented. In Section 5.1 a clinical study of infants undergoing cardiac surgery is presented with emphasis on the practical problems of respiratory function testing in intubated infants. Sections 5.2-5.4 are methodological studies into newer equipment for the assessment of intubated infants.

The following publications have resulted from this work:


5.1 A pilot study of the effect of cardiopulmonary bypass on respiratory compliance in infants and young children

5.1.1 Introduction and aims

Open heart surgery with cardiopulmonary bypass is required to correct most forms of serious congenital heart disease. Cardiopulmonary bypass in children, using hypothermia with crystalloid haemodilution, is associated with capillary leak, which results in an increase in total body water. This water, which is largely in the extravascular fluid compartment, is known to have an adverse effect on major organ function. A number of strategies have been applied to reduce this accumulation of body water, one of the most successful being modified ultrafiltration (MUF) as described by Naik et al in 1991. MUF is carried out in the first 10-15 minutes after the cessation of bypass, with blood being taken from the aortic cannula and returned after ultrafiltration to the right atrium.

One of the organs adversely affected by cardiopulmonary bypass is the lung. Open heart surgery in infants has been reported to reduce respiratory compliance. The mechanism for this change is not fully determined but pulmonary oedema and pulmonary sequestration of white cells have been implicated. If a significant proportion of this adverse change in compliance was due to pulmonary oedema, then MUF might improve respiratory mechanics. At the time of this thesis a randomised controlled study to examine the effects of MUF on haemodynamic and immunological parameters was planned at the Hospital for Sick Children, and the Respiratory Unit was invited to examine the effect of MUF on respiratory function in the same patient population. The sample size and patient population were primarily chosen to allow investigation of body water and cytokine production. The sample size (10 in each group), while not being sufficient for a definitive study of the effect of MUF on respiratory compliance, allowed a pilot study to assess the feasibility of determining the effect of different forms of cardiopulmonary bypass on respiratory compliance in infants and young children undergoing cardiac surgery.

5.1.2 Materials and methods

5.1.2.1 Subjects

Infants and children requiring cardiopulmonary bypass (CPB) for the surgical
correction of cardiac lesions associated with left to right shunt were recruited to the study. Neonates (i.e. age less than 4 weeks) and infants weighing less than 3 kg were not eligible.

5.1.2.2 Protocol

Subjects were randomised to 2 groups; a group that received MUF immediately post-bypass and a control group.

After induction of anaesthesia the subjects were paralysed with pancuronium, intubated and ventilated using 33% oxygen in nitrous oxide. Anaesthesia was maintained with fentanyl and up to 0.5% halothane or isoflurane. Respiratory mechanics were measured in the anaesthetic room prior to surgery. Surgery with CPB was performed using standard techniques. Immediately post-bypass MUF was used in the treatment group.

Further respiratory mechanics measurements were made postoperatively in the intensive care unit. Measurements were attempted 2 hours, 6 hours and 10 hours following discontinuation of cardiopulmonary bypass provided the subject remained intubated. Postoperative care was determined by the intensivist. All subjects received morphine by infusion (10-40 \( \mu \)g·kg\(^{-1}\)·hour\(^{-1}\)) but additional sedation and muscle relaxants were only used if clinically indicated and not for the sole purpose of facilitating research. No measurements were made after extubation.

Volume controlled ventilation using a Servo 900C ventilator (Siemens Elema, Sweden) and standard settings was used during the respiratory measurements. The ventilator settings were adjusted to achieve measured tidal volumes of 10 (±1) mL·kg\(^{-1}\) with a positive end expiratory pressure (PEEP) of 3-5 cmH\(_2\)O, a respiratory rate of 20 or 25 per minute (depending on subject weight) and an I:E ratio of 1:2. In the postoperative period, some subjects were weaned to synchronised intermittent mandatory ventilation (SIMV). During measurements of respiratory mechanics these subjects were returned to full ventilation. If this was unsuccessful measurements were attempted during spontaneous breathing. Tracheal suction was performed prior to measurements in the postoperative period and in any subject with clinical evidence of secretions in the pre-operative period. All subjects received 3 large breaths prior to
measurements to minimise atelectasis and facilitate recognition of any leak around the
tracheal tube. Gentle cricoid pressure was used as necessary to abolish the leaks
around the tracheal tube during the measurements.

5.1.2.3 Measurement methods
Respiratory mechanics were assessed by measuring;
- dynamic respiratory compliance and resistance using multiple linear regression
  (MLR) (Section 3.2.1.2.2)
- static respiratory compliance using the multiple interrupter (MIT) and multiple
  occlusion technique (MOT) (Sections 3.2.3.2 and 3.2.3.1)
The measuring apparatus consisted of a spring loaded shutter, operated by a cable
release and incorporating a pressure port, connected to a Fleisch size 0 or 1 pneumo-
tachograph depending on the size of the infant. Calibration was performed using
appropriate gas mixtures. The apparatus was connected between the tracheal tube and
the ventilator tubing. Data were sampled at 200 Hz and collected and processed using
an IBM compatible computer and RASP software. For further details of the
equipment, calibration techniques and data processing see Sections 3.2.4, 3.1.2.3.1
and 3.1.2.3.2 respectively.

As oesophageal pressure was not being measured dynamic respiratory mechanics
measurements were only possible during positive pressure ventilation when the infant
was not making respiratory efforts. Data were collected in 72 second epochs. The data
were analysed using MLR and a single compartment linear model as described in
Section 3.2.2. Results are reported as the mean of 10 consecutive breaths.

Static respiratory mechanics measurements were attempted during IPPV using the
multiple interrupter technique (MIT). In infants making respiratory efforts the
multiple occlusion technique was attempted during spontaneous ventilation if it was
not possible to suppress the respiratory efforts using IPPV. Data were analysed as
described in Section 3.2.4. The mean of 3 satisfactory measures using MIT is
reported.

Comparisons between the two techniques of assessing compliance were made using
the method of Bland and Altman. As the range of values was wide because of the
Table 5.1.1: Subject details

<table>
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<tr>
<th>Subject no.</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age months</th>
<th>Length cm</th>
<th>Weight kg</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>VSD, ASD, PDA</td>
<td>F</td>
<td>3</td>
<td>56.3</td>
<td>4.2</td>
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<tr>
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<td>M</td>
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<td>M</td>
<td>3</td>
<td>56.0</td>
<td>4.2</td>
</tr>
<tr>
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<td>M</td>
<td>4</td>
<td>55.2</td>
<td>3.5</td>
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<td>5</td>
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<td>M</td>
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<td>62.5</td>
<td>5.3</td>
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<td>5</td>
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<td>F</td>
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<tr>
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<td>AVSD, Down’s</td>
<td>M</td>
<td>4</td>
<td>64.3</td>
<td>5.3</td>
</tr>
<tr>
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<td>8</td>
<td>65.3</td>
<td>4.8</td>
</tr>
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<td>M</td>
<td>16</td>
<td>73.9</td>
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</tr>
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<tr>
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<td>TOF††</td>
<td>M</td>
<td>64</td>
<td>104.0</td>
<td>16.3</td>
</tr>
</tbody>
</table>

VSD; ventriculo-septal defect, ASD; atrio-septal defect, PDA; patent ductus arteriosus, AVSD; atrio-ventriculo-septal defect, AP; aorto-pulmonary, AI; aortic incompetence, TOF; Tetralogy of Fallot.

† left to right shunt at catheter but mild polycythaemia, †† left to right shunt at catheter.
large age range of the subjects studied, percentage differences relative to the mean estimate of $C_n$ obtained with the two methods were used when calculating 95% limits of agreement.

5.1.3 Results

Twenty subjects were recruited to the study and respiratory function testing was attempted in 16 subjects. Measurements were not attempted in the other subjects because the author was not available (3 subjects) or the presence of chronic lung disease required prolonged preoperative ventilation (1 subject). Details of the 16 subjects are given in Table 5.1.1.

5.1.3.1 Preoperative respiratory function

Respiratory mechanics by multiple linear regression (MLR) were obtained in all subjects. The $r^2$ values for MLR ranged from 0.952 to 0.996 (group mean 0.985). Values for $C_n$ and $R_n$ plotted against length are shown in Figure 5.1.1. Normal ranges published by Lanteri and Sly are also shown. Respiratory compliance was also assessed in 15 subjects using the multiple interrupter technique (MIT). The $r^2$ values for MIT ranged from 0.993 to 0.999 (group mean 0.997). In the remaining subject the shutter failed. A comparison of the results obtained for $C_n$ using the two methods is shown in Figure 5.1.2. The mean difference between the two methods ($100 \cdot (\text{MIT} - \text{MLR})/0.5 \cdot (\text{MIT} + \text{MLR})$) was 3.6%, 95% limits of agreement $-13.2\%$, $20.4\%$. In 11/15 subjects static $C_n$ exceeded dynamic $C_n$. In only one subject (subject no.4) was dynamic $C_n$ more than 5% greater than static $C_n$.

5.1.3.2 Postoperative respiratory function

5.1.3.2.1 Early postoperative

Measurements were attempted in 14 subjects between 110 and 180 minutes post-bypass. One subject had been extubated in the operating theatre and the author was not available in the other case. At the time of the measurements 7 patients had clinical evidence of drug induced paralysis. Respiratory mechanics by MLR were obtained in all the paralysed subjects but in only 5/7 unparalysed subjects, there being evidence of respiratory effort in the other 2 subjects. Measurements of $C_n$ using MIT were
Figure 5.1.1: Preoperative respiratory mechanics

a) Preoperative respiratory compliance and b) Preoperative respiratory resistance for the control and MUF groups plotted with normal data from Lanteri and Sly.158
Figure 5.1.2: Comparison of MIT and MLR for the measurement of preoperative respiratory compliance

The difference in $C_{rs}$ between the two methods (MIT – MLR) expressed as a percentage plotted against the mean for the two methods. The solid and dashed lines represent the mean difference and 95% limits of agreement. Open triangles; control group, closed triangles; MUF group.

Figure 5.1.3: Pre and postoperative respiratory mechanics

a) Respiratory compliance and b) respiratory resistance pre and postoperatively. Open triangles; control group, closed triangles; MUF group.
successful in all paralysed and 3/7 unparalysed subjects. The paired results for pre- and early postoperative $C_n$ and $R_n$ are shown in Figures 5.1.3a) and 5.1.3b) respectively. It is apparent from the table of subject details and these plots that the smallest infants (i.e. those with the lowest compliance) were mainly randomised to the control group. The 3 subjects with the highest initial values of $C_n$ showed the largest falls in $C_n$.

5.1.3.2.2 Late postoperative
By 6 hours one further patient had been extubated and only one patient had clinical evidence of residual paralysis which had resolved by 10 hours. Respiratory function measurements at 6 and 10 hours post bypass had a high failure rate. At 6 hours successful measurements of both MLR and MIT were only obtained in 4/13 children and MLR or MIT in 1 further subject each. At 10 hours MLR and MIT were both successful in only 3/13 attempts with assessments of MLR or MIT in 1 further subject each. Occasional patients were insufficiently relaxed for MIT during IPPV but relaxed for single occlusions during periods of spontaneous ventilation which would have allowed a measure of $C_n$ using the multiple occlusion technique.

The agreement between the measures of $C_n$ obtained using MLR and MIT in unparalysed subjects obtained in the postoperative period is shown in Figure 5.1.4. The mean difference between the methods ($\frac{100\cdot (\text{MIT} - \text{MLR})}{0.5\cdot (\text{MIT} + \text{MLR})}$) was 4.5%, 95% limits of agreement −13.4%, 22.5%. In 7/9 pairs of measurements static $C_n$ was greater than dynamic $C_n$. In only 1 subject (subject no.11) was dynamic $C_n$ more than 5% greater than static $C_n$.

5.1.4 Discussion
Preoperative $C_n$ and $R_n$ values were related to infant length which explains the very wide range of values found. Normative values of dynamic respiratory compliance obtained during IPPV under anaesthesia by Lanteri and Sly\textsuperscript{188} suggest that the smallest infants in this study had low respiratory compliance. A low compliance and high resistance have been reported in other studies of infants with left to right shunt congenital heart disease and a correlation found between measures of excessive pulmonary blood flow and the severity of the abnormalities of the mechanics
measurements. Those infants that require surgery in early life have more serious disease with higher pulmonary blood flows than older, often asymptomatic, children.

Both MLR and MIT were satisfactory methods of assessing $C_n$ in paralysed preoperative infants but both methods had a low success rate in the postoperative period once the effects of muscle relaxants and general anaesthesia had resolved. This was as a result of patient efforts or in some infants marked restlessness when disturbed.

A comparison of the two measurement methods in both paralysed preoperative and unparalysed postoperative patients for the measurement of $C_n$ showed reasonable agreement in most subjects, with values obtained using MIT usually greater than those obtained using MLR particularly in the smaller infants. Examination of the MIT data showed that in many subjects the volume pressure relationship was not linear over the entire tidal volume range with $C_n$ being lower at high lung volumes. This explains why MLR based on data collected throughout the whole breath may give a lower estimate $C_n$. 

![Figure 5.1.4: Comparison of MIT and MLR for the measurement of postoperative respiratory compliance](image)
The older asymptomatic children showed the largest falls in $C_r$ (Figure 5.1.3) in the early postoperative period. The potential beneficial effect of surgery on $C_r$ by reducing pulmonary blood flow in such subjects is likely to be small relative to the adverse effects of bypass and sternotomy. In contrast, in the smaller sicker infants with higher pulmonary blood flow the beneficial effect of a reduction in pulmonary blood flow is likely to outweigh the deleterious effects of bypass and sternotomy.\textsuperscript{192}

5.1.5 Conclusions
This pilot study suggests that for the effects of MUF on respiratory function to be determined, methods of reliably measuring mechanics in unparalysed infants would be necessary, or a study design devised in which all data were obtained intra-operatively when the subjects were fully paralysed. The latter option would also avoid confounding postoperative factors such as differences in the postoperative management of fluids. Standardisation of anaesthesia and intra-operative fluid management would also be desirable. However, the apparatus used for this pilot study would not be suitable for intra-operative measurements because of its bulky nature. In addition, stratification of the subjects to avoid most of the smaller and therefore sicker infants falling in the same treatment group would be desirable as it is established that the increase in body water is most marked in the smallest infants undergoing the longest bypass periods.\textsuperscript{183}
5.2 An assessment of the Capnomac Ultima™ for continuous monitoring of respiratory parameters during IPPV in infants and young children

5.2.1 Introduction and aims

Measurements of ventilator parameters and respiratory mechanics during IPPV in infants and young children undergoing surgery have both research and clinical monitoring applications. The 1989 NCEPOD (National Confidential Enquiry into Perioperative Deaths) report recognised the desirability of continuous monitoring of tidal volumes when infants are ventilated with the Nuffield Penlon anaesthetic ventilator. ¹⁹⁴

In 1991 Datex (Helsinki, Finland) developed the side stream spirometer™ to allow continuous monitoring of pressure, flow and volume changes during mechanical ventilation in the operating theatre. This development was incorporated into their anaesthetic gas monitoring equipment and became available as the Capnomac Ultima™. The original version was developed for use in adults and children weighing over 20 kg. In 1993 a new version of the monitor, with a more compact sensor unit (dead space 2.5 mL) and modified software for use in smaller children (3-20 kg), was developed. This monitor was made available to the Portex Department of Paediatric Anaesthesia for clinical assessment. Although primarily developed for monitoring, the device claimed to measure respiratory mechanics and was therefore also of potential interest for research studies.

The aims of this study were to:

• compare airway pressure and volume measurements, and measures of respiratory mechanics obtained with the Datex side arm spirometer™ with those obtained using Fleisch pneumotachographs and Validyne transducers
• assess ease of use of the Datex side arm spirometer™ during IPPV in infants and young children receiving general anaesthesia

5.2.2 Materials and methods

5.2.2.1 Measurement methods

The Datex side arm spirometer™ (Figure 5.2.1) consists of a sterilisable flow meter
Figure 5.2.1: The Capnomac Ultima™ D-Lite™ sensor

- Sampling line for gas analysis
- 15mm male connector (for breathing system)
- 15mm female connector (for tracheal tube)
- Pressure ports
- Connecting tubing to pressure sensors
(the D-Lite™ sensor) with two pressure ports such that both the pressure difference between the two ports and the pressure at the airway opening can be measured. Each port is attached to the monitor, which contains two piezoresistive semiconductor sensors, by a 3 m length of 3 mm internal diameter tubing. A separate port connects to a sampling line. Gas is sampled at 200 mL·min⁻¹ for measurement of oxygen concentration using a paramagnetic oxygen sensor, and nitrous oxide, carbon dioxide and anaesthetic gas concentrations by infra-red spectroscopy. For clinical use the manufacturer recommends calibration at 6 monthly intervals. The equipment was calibrated once at the start of the study by applying a known volume signal using a calibrated syringe (Hans Rudolph) in accordance with the manufacturer’s protocol. Although the apparatus was not recalibrated for each subject, a calibration check was performed by syringing 100 mL of air into and out of the D-Lite™ and recording the measured volume prior to each study. Data collection for this study was completed over a 5 month period. The D-Lite™ sensor is compatible with standard 15 mm tracheal tube connectors and breathing systems.

The pressure difference between the two ports of the side arm spirometer is related to flow and depends on the density of the gas as well as the geometry of the spirometer. The analog signal is digitised, linearised and corrected for gas density, which is calculated from the measured gas composition. The manufacturer claims that volume measurements under typical conditions should be within ±6% with a resolution of 1 mL and pressure measurements should be within ±1.5 cmH₂O with a resolution of 1 cmH₂O from -20 to +80 cmH₂O. The Datex monitor processes the data to measure inspiratory and expiratory tidal volume and minute volume, peak and plateau airway pressure, and expiratory:inspiratory time ratio (see Figure 5.2.2 for manufacturer’s definitions). Real time pressure and flow waveforms as well as pressure-volume and flow-volume loops can be displayed. The respiratory compliance and the percentage of tidal volume expired in the first second of expiration are calculated as parameters of respiratory function. The device can be set to alarm when values fall outside user defined limits. Displayed data can be recorded using software provided by the manufacturer and an IBM compatible PC.

The effective dead space of the D-Lite™ sensor was measured by adding the sensor to
Figure 5.2.2: Respiratory parameters as defined by the Capnomac Ultima™

Example of Flow and Pressure Waveforms

- Ppeak = maximum pressure
- Pplat = plateau pressure = end inspiratory pressure
- PEEP = end expiratory pressure

Calculation Formulas

\[ V1.0 = \left( \frac{\text{volume expired during the first second}}{TV_{\text{exp}}} \right) \times 100\% \]

\[ C = \frac{TV_{\text{exp}}}{(P_{\text{plat}} - P_{\text{EEP}})} \]

\[ I : E \text{ ratio} = 1: \left( \frac{\text{expiration time}}{\text{inspiration time including pause}} \right) \]

a Portex 15 mm tracheal tube connector and 15 mm catheter mount and measuring the increase in volume by filling with water. The resistance of the D-Lite™ sensor was assessed using known flows of air from calibrated rotameters applied in both the inspiratory and expiratory directions.

Measurements of flow, volume and airway pressure were also made using heated Fleisch size 0 (weight < 10 kg) or 1 (weight ≥ 10 kg) pneumotachographs (PNTs) and
Validyne pressure transducers. Data were sampled at 200 Hz and displayed and recorded using RASP software and an IBM compatible PC. Full details of the equipment are given in Section 3.1.2. The PNT was calibrated for each study using 100 mL aliquots of the same gas mixture as that used to ventilate the infant. A Hans Rudolph calibration syringe was used. Airway pressure was calibrated using a water manometer.

5.2.2.2 Subjects
Infants and young children weighing less than 20 kg, without clinical features of respiratory disease, who required anaesthesia with tracheal intubation for elective surgery were eligible for the study.

5.2.2.3 Protocol
Anaesthesia was induced and the trachea intubated with the aid of muscle relaxants. Plain, armoured or RAE pattern Portex tracheal tubes were used depending on the anaesthetist’s preference and surgical requirements. After tracheal intubation the leak around the tracheal tube and tracheal tube position were assessed during a period of manual ventilation. Subjects were then ventilated using an Ayre’s T-piece and Nuffield Penlon ventilator with Newton valve. A fresh gas flow of 3, 4.5 or 6 L·min⁻¹ was used according to the size of the infant and the preference of the anaesthetist. Subjects were ventilated using 33% oxygen in nitrous oxide and anaesthesia maintained using 0.5-1% halothane or isoflurane. The ventilator settings were adjusted to give satisfactory chest expansion and a clinically appropriate respiratory rate as judged by the anaesthetist responsible for the patient. Leak of gas around the tracheal tube was classified as absent (no leak detected during hand or mechanical ventilation), clinically insignificant (leak only audible at pressures greater than those used for ventilation) or large (leak audible during mechanical ventilation). All subjects were paralysed with non-depolarising muscle relaxants (atracurium, curare or vecuronium) prior to the measurements. Measurements were made, prior to surgery, using the side arm spirometer and the reference apparatus which were connected to the breathing circuit in turn. The order of the two measurements was randomised. No alterations were made to the ventilator or anaesthetic machine between the two sets of measurements and care was take to avoid moving the child or tracheal tube between
the two sets of measurements. A period of two minutes was allowed after connecting each piece of apparatus before collecting data. Sufficient data were collected using the Capnomac to allow analysis of 10 breaths (≈ 3 minutes for the software program to export data from 10 breaths). Using RASP software 10 consecutive breaths could be analysed and only 2 epochs each of a minimum of 10 breaths were recorded. Subject length was then measured and the patient transferred to theatre. In some subjects the Capnomac was used as a clinical monitor during surgery. Any difficulties with setting up, or using the Capnomac Ultima™, both during data collection and intra-operatively were noted.

5.2.2.4 Data analysis

Data from the Capnomac software program were saved as Lotus 123 files. Mean values for 10 breaths for each of the measured parameters were calculated using Lotus 123.

Data collected using RASP were exported to Anadat™ for analysis. Ten consecutive breaths were analysed. The % of the total expired tidal volume expired in the first second ($V_{1.0}$) and dynamic respiratory compliance calculated by the Mead-Whittenberger method (Section 3.2.1.2.1) were determined for the same 10 breaths by manual analysis.

5.2.2.5 Statistical analysis

Comparisons between the two measurement methods were made using the method of Bland and Altman.³³³

5.2.3 Results

5.2.3.1 In vitro assessment of the D-Lite™ sensor

The dead space of the D-Lite™ sensor was 2.6 mL. The resistance of the D-Lite™ sensor measured using air in the inspiratory and expiratory direction was as given in Table 5.2.1. The resistance of a Fleisch size 0 PNT is 0.43 kPa·L⁻¹·s, and of a size 1 PNT is 0.10 kPa·L⁻¹·s at 100 mL·s⁻¹.

5.2.3.2 In vivo assessment of the Capnomac Ultima™

Thirty five subjects were recruited for the study and data obtained from 30. One
Table 5.2.1: Resistance of the D-Lite™ sensor

<table>
<thead>
<tr>
<th>Flow mL·s⁻¹</th>
<th>Inspiratory resistance kPa·L⁻¹·s</th>
<th>Expiratory resistance kPa·L⁻¹·s</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.30</td>
<td>0.39</td>
</tr>
<tr>
<td>100</td>
<td>0.42</td>
<td>0.54</td>
</tr>
<tr>
<td>150</td>
<td>0.48</td>
<td>0.66</td>
</tr>
<tr>
<td>200</td>
<td>0.59</td>
<td>0.77</td>
</tr>
<tr>
<td>300</td>
<td>0.79</td>
<td>0.99</td>
</tr>
<tr>
<td>400</td>
<td>1.00</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Table 5.2.2: Subject details

| Male:Female | 18:12 |
| Age, months, median (range) | 6.0 (0.4-59.5) |
| Weight, Kg, median (range) | 7.4 (3.1-14.5) |
| Length, cm, median (range) | 69 (51-98) |

Operation was cancelled, one child was withdrawn before the study commenced, two sets of data were lost due to computing problems and one set of data could not be analysed due to a very large leak around the tracheal tube. Demographic details are given in Table 5.2.2. Subjects were scheduled for ophthalmic, urological, plastic, orthopaedic, general surgical or neurosurgical procedures. Tracheal tube size ranged from 3.0 to 5.5 mm internal diameter.

5.2.3.2.1 Calibration checks

The group mean (range) inspiratory volume recorded by the Datex monitor when tested prior to measurements in each subject using aliquots of 100 mL of air was 101 mL (95-107 mL). The group mean (range) expiratory volume was 98 mL (96-101 mL).

5.2.3.2.2 Tidal volume measurements

The agreement between the two measurement methods for inspiratory and expiratory
tidal volumes was determined using the methods of Bland and Altman. In view of the wide age range and therefore range of tidal volumes, the difference between the two methods was expressed as a percentage of the mean measurement obtained using the two methods. Data are shown in Figure 5.2.3. The mean difference (95% limits of agreement) for the two methods (Fleisch – Capnomac) for inspiratory tidal volumes was 4.4% (−12.2, 20.9%) and for expiratory tidal volumes was 15.4% (−0.8, 31.5%). When data obtained from the 12 infants without a detectable leak around the tracheal tube were analysed separately, values of 1.7% (−17.6, 21.0%) and 13.8% (3.2, 24.5%) were obtained for inspiratory and expiratory tidal volumes respectively.

Two comparisons of the measurement methods were made in 5 subjects and three comparisons in 1 subject. On five occasions gentle cricoid pressure was applied to reduce the leak around the tracheal tube, on one occasion the tracheal tube was exchanged for a larger tube with less leak, and on one occasion the ventilator settings were altered. Data are shown in Figure 5.2.4 plotted as percentage change detected using the Fleisch PNT against percentage change detected using the Capnomac for both inspiratory and expiratory tidal volumes. On all 7 occasions the percentage change in inspiratory tidal volume was tracked within 10%. The percentage changes in expiratory tidal volume were less well tracked with large discrepancies (29 and −58%) in two of the subjects both of whom had increased tidal volumes after application of cricoid pressure.

5.2.3.2.3 Airway pressure measurements

Peak inspiratory pressures ranged from 13.0 to 26.8 cmH₂O measured using the Validyne pressure transducer. The mean within-subject difference (95% limits of agreement) for the two methods (Validyne – Capnomac) for peak inspiratory pressure was 1.6 cmH₂O (−0.1, 2.3 cmH₂O).

Positive end expiratory pressure (PEEP) ranged from 0.2 to 3.1 cmH₂O measured with the Validyne pressure transducer. The mean within-subject difference (95% limits of agreement) for the two methods (Validyne – Capnomac) of measuring PEEP was 0.2 cmH₂O (−0.3, 0.7 cmH₂O).
Figure 5.2.3: Comparison of the Capnomac Ultima™ and Fleisch PNT for the measurement of a) inspiratory and b) expiratory tidal volumes

The difference in $V_T$ between the two methods (Fleisch PNT – Capnomac) expressed as a percentage plotted against the mean for the two methods. The solid and dashed lines represent the mean difference and 95% limits of agreement.\textsuperscript{133}
Figure 5.2.4: Comparison of the Capnomac Ultima™ and Fleisch PNT for detecting changes in tidal volumes

Percentage change in inspiratory and expiratory tidal volumes measured with a Fleisch PNT plotted against the percentage change in inspiratory and expiratory tidal volume measured with Capnomac Ultima™. The tidal volume was altered by reducing the leak around the tracheal tube or altering ventilator settings.

5.2.3.2.4 Respiratory timing measurements

The Capnomac Ultima™ calculates respiratory rate from the expired carbon dioxide signal rather than the output of the side arm spirometer. Therefore respiratory rate data have not been compared.

The E:I ratio ranged from 1.5 to 3.4 measured using the Fleisch PNT. The mean
difference (95% limits of agreement) for the two methods (Fleisch – Capnomac) for E:I ratios was 0.2 (−0.3, 0.7).

### 5.2.3.2.5 Respiratory function indices

The Capnomac displays a value for total respiratory compliance during positive pressure ventilation irrespective of whether or not there is a leak of air around the tracheal tube. Compliance is calculated from expired tidal volume and airway pressure (Figure 5.2.2). Values are displayed as mL·cmH₂O⁻¹ to the nearest whole number. As mechanics can only be measured reliably in the absence of a tracheal tube leak, comparison between the two measurement methods was limited to the 12 subjects without a detectable tracheal tube leak. Dynamic compliance was calculated using the expired tidal volume and airway pressure at the points of zero flow (Mead-Whittenberger technique see Section 3.2.1.2.1). Compliance ranged from 1.8 to 13.5 mL·cmH₂O⁻¹ measured using the Fleisch and Validyne. In the smallest baby (weight 3.1 kg) the Capnomac displayed a negative value. That infant’s data were excluded from the comparison of methods. The mean difference (95% limits of agreement) for the two methods (Fleisch – Capnomac as a % of the mean value) for compliance was 19.0% (−5.1, 43.1%).

The Capnomac also measures $V_{1.5}$, the percentage of tidal volume expired in the first second of expiration. $V_{1.5}$ measured by analysing the data obtained using the Fleisch PNT ranged from 61 to 100%. Good agreement was obtained between the two measurement methods, the mean within-subject difference (95% limits of agreement) was −1.4% (−9.5, 6.7%) (Fleisch – Capnomac).

### 5.2.3.2.6 Ease of use of the Capnomac Ultima™

The research personnel and the clinicians involved in the care of the patients found the monitor easy to set up and use. The sensor was easy to connect to and disconnect from a standard 15 mm tracheal tube. It was lightweight and did not drag on the tracheal tube. The alarms were simple to use. Users had no difficulty displaying continuous time based data and examining flow-volume and volume pressure loops (Figure 5.2.5). Data were stored in the memory of the monitor and users were able to display trends in the measured parameters. Meaningless values of compliance (i.e.
Figure 5.2.5: The Capnomac Ultima™ display

Screen appearances of the Capnomac Ultima™ during intermittent positive pressure ventilation in a 3.1 kg two week old infant. a) Time based trace of flow, pressure and partial pressure of carbon dioxide. b) Flow-volume curve. c) Volume-pressure curve. The images are shown as black on white rather than white on black for clarity.
negative values) were occasionally displayed particularly in the smallest patients, with large tracheal tube leaks. The monitor usually stated that a tracheal tube leak was present even when it could not be detected clinically.

5.2.4 Discussion

The Capnomac Ultima™ provided a continuous, easy to use, time based display of flow, volume and airway pressure with automatic calculation and display of inspiratory and expiratory tidal volume, peak airway pressure, end inspiratory (plateau) pressure and PEEP. Data could also be displayed as flow-volume and pressure-volume loops.

Comparison of the tidal volume measurements with those obtained by analysis of the flow data obtained with a Fleisch PNT and Validyne pressure transducer, during positive pressure ventilation, showed 95% limits of agreement that exceeded those expected from the manufacturer’s statement that typical accuracy was within ±6%. For both inspiratory and expiratory tidal volume measurements, the Capnomac underestimated tidal volume (mean underestimate 4% and 15% respectively). The much greater underestimate of tidal volume during expiration explains the reported tracheal tube leak by the Capnomac in the absence of a clinically detectable leak. Agreement between the airway pressure measurements was much better than for tidal volume measurements, 95% limits of agreement being -0.1, 2.3 cmH₂O at pressures up to 27 cmH₂O.

A potential problem with the study design was that the measurements with the Capnomac and PNT were sequential rather than simultaneous. This was because the combined dead space and resistance of the two measuring devices were considered unacceptable. There was also concern that the addition of the Fleisch PNT in series with the Capnomac might make the flow pattern within the D-Lite™ sensor more laminar resulting in greater accuracy than would be achieved in the clinical setting. By making the measurements sequentially it is possible the tidal volumes may have been slightly different. The tidal volumes and airway pressures obtained would be expected to depend on the ventilator settings, respiratory mechanics, resistance of the measuring device and any loss of gases from the breathing system. However, the
ventilator was not altered between measurements. Furthermore, since all subjects were free of respiratory disease and ventilated with the aid of muscle relaxants, respiratory mechanics would be expected to be stable over the short period of time required for both measurements. The resistance of the D-Lite™ sensor was flow dependent, but at flows of 100-200 mL·s⁻¹ was similar to that of the Fleisch size 0 PNT used in the smaller subjects. The resistance was greater than that of the Fleisch size 1 PNT especially at higher flows. The effect of resistance would therefore be expected to be greatest in the subjects with the larger tidal volumes. Figure 5.2.3 does not show this to be the case. Care was taken to minimise movement of the tracheal tube during the paired measurements to avoid alterations of the magnitude of any tracheal tube leak. In addition the analysis of the data obtained from those subjects without a clinically detectable tracheal tube leak gave similar results to those for the whole group of subjects. True differences in tidal volume during the 2 sets of measurements are therefore unlikely to explain the findings and certainly could not explain the observed difference between expiratory and inspiratory tidal volumes when using the Capnomac.

It is possible that more accurate tidal volume measurements would have been obtained if the Capnomac had been calibrated attached to the appropriate tracheal tube for each subject. It was not the purpose of this study to explore the maximum accuracy obtainable. Calibrating for each subject would detract from the clinical value of the Capnomac. The manufacturer states that for the adult version inspiratory volumes are overestimated when using a Bain breathing system but that this can be corrected by using a filter between the D-Lite™ sensor and the breathing system. It is possible that filtering would also improve the measurements obtained when using an Ayre’s T-piece and Nuffield Penlon ventilator.

In the clinical setting tidal volume measurements within ±15% may be valuable in warning of significant changes. The data presented in Figure 5.2.4 suggests the monitor is capable of tracking changes in tidal volume in individual subjects which, clinically, may be of more relevance than absolute values. The accuracy of the airway pressure measurements was adequate for clinical purposes. Accuracy at airway pressures over 30 cmH₂O could not be assessed in the subjects studied. In contrast to
the intensive care setting such high pressures are rarely required in anaesthetic practice.

The Capnomac provided two indices of respiratory function, total respiratory compliance and $V_{1.0}$, the percentage of tidal volume expired in the first second. The presence of a tracheal tube leak (18/30 subjects) would make respiratory compliance measurements unreliable in the majority of subjects. The Capnomac underestimated compliance which is to be expected as it underestimated expired tidal volume. The algorithm used is not ideal as it is based on zero flow points being identified (Section 6.4.2.2). Clinicians would need to be careful in their interpretation of the Capnomac compliance parameter. Good agreement was obtained between the two measurements of $V_{1.0}$, the percentage of tidal volume expired in the first second. However this parameter is likely to be a less useful indication of respiratory resistance in children than adults because they are ventilated at higher respiratory rates with shorter expiratory times. A value of 100% will always be obtained when the expiratory time is 1 s or less. Since this study was completed the manufacturer has modified the software to calculate $V_{e}$, when in paediatric mode.

5.2.5 Conclusions

The Capnomac Ultima™ was easy to use in small (3-20 kg) infants. Comparison with a Fleisch PNT and Validyne pressure transducers suggests clinically useful information about tidal breathing parameters can be obtained during IPPV. However care should be taken when interpreting the parameters of respiratory function. The quantitative accuracy of the data obtained limits the research potential of the monitor. Nevertheless the concept of a device that measures gas composition permitting automatic adjustment of calibration when gases other than air are used is a potential advance when making measurements during anaesthesia and in intensive care.
5.3 The assessment of neonatal pulmonary monitors

This section is divided into two parts. The in vitro and in vivo assessment of neonatal pulmonary monitors are covered in Sections 5.3.1 and Section 5.3.2 respectively.

5.3.1 The in vitro assessment of neonatal pulmonary monitors

5.3.1.1 Introduction and aims

Commercially available automated pulmonary monitors are being increasingly used in neonatal intensive care units. However, detailed information regarding the static and dynamic accuracy of these monitors is rarely available. The American Thoracic Society has established technical standards and testing procedures to ensure that equipment used for spirometric measurements in older subjects is capable of providing a reasonable level of accuracy. Such standards do not exist for neonatal monitoring equipment and the manufacturers' assessment of equipment prior to marketing is frequently either less extensive than might be desired or the technical detail to attest to the accuracy of the equipment is unavailable. There are a number of potential sources of errors in equipment. The commonest ones are that the actual measuring device does not have a predictable output for a known input over the full range of flow and pressure seen in clinical practice (inaccurate calibration), the frequency response of the equipment is inadequate to follow a rapidly changing signal accurately, and that the computer algorithms used in calculating results are either incorrect, or not applicable to the situation in question.

The aim of this study was to develop a laboratory protocol to evaluate the static and dynamic accuracy of neonatal pulmonary monitors. The protocol aimed to;

- assess the static accuracy and frequency response of the measuring devices incorporated in a pulmonary function monitor (flow, airway and oesophageal pressure) both alone and assembled as intended for use with a tracheal tube
- assess the application of computer algorithms for on-line calculation of mechanics
- assess the apparatus in use during intermittent positive pressure ventilation (IPPV) of a neonatal lung model

A recently released monitor the Bicore CP100 (software version 3.3) was selected for the development of the protocol.
Figure 5.3.1: The Bicore CP100

a): The monitor, b): flow transducer, c): flow transducer and occlusion valve and d): oesophageal balloon shown next to a larger commercially available infant oesophageal balloon (Peds).
5.3.1.2 Materials and methods

The Bicore CP100 (software version 3.3) (Bicore Monitoring Systems, Irvine, CA) (Figure 5.3.1) consists of a disposable, pre-calibrated, low dead space, variable orifice flow transducer with a pressure port each side of the variable orifice such that both the differential pressure across the screen and the pressure at the airway opening ($P_{aw}$) can be measured. Each pressure port is attached to the monitor, which contains two pressure transducers, by a 1.13 m length of 2 mm internal diameter (i.d.) tubing. The flow transducer is compatible with standard 15 mm tracheal tube connectors. The manufacturer states an effective dead space of less than 1 mL and a working range of 0-500 mL·s$^{-1}$. A disposable occlusion valve that connects between the flow transducer and the ventilator circuit is also available.

Oesophageal pressure ($P_{oes}$) is measured using a disposable 25 mm balloon mounted on a stiff 30 cm tube of 1.1 mm i.d.. This is connected to the monitor by a 1.22 m length of stiff tubing of 1.3 mm i.d. The coefficient of displacement of the transducer is 0.022 mL·kPa$^{-1}$ ($= 0.00219$ mL·cmH$_2$O$^{-1}$ manufacturer's data). The balloon is also factory calibrated and the degree of inflation is computer controlled, with the operator having a choice between 5 incremental filling volumes.

Flow and pressures are sampled at 100 Hz. The Bicore monitor displays values for respiratory rate, inspired and expired tidal volumes, peak inspiratory and expiratory flows, inspiratory and expiratory times, % tube leak and expired minute volume. Values are given for both ventilator and spontaneous breaths. For the ventilator breaths alone, total respiratory dynamic compliance ($C_{r, dyn}$) and resistance ($R_{r}$), and dynamic compliance over the terminal 20% of inspiration, expressed as a ratio of compliance over the whole breath ($C_{20}/C_{dyn}$),$^{197}$ are displayed. Pressures are given in centimetres of water. There is a choice of averaging over 1, 10 or 30 breaths. In addition, when the oesophageal balloon is in use, transpulmonary pressure is calculated as the difference between $P_{oes}$ and $P_{aw}$ and values for lung mechanics are displayed. The occlusion valve is intended for the measurement of passive respiratory mechanics during spontaneous and ventilator breaths.

The flow, $P_{aw}$ and $P_{oes}$ measuring devices were evaluated for static measurement
accuracy and frequency response. The resistance of the flow transducer, both alone and when connected to the occlusion valve, was determined. Then, using a neonatal lung model, the values of tidal breathing parameters displayed by the Bicore CP100 were compared to those calculated independently from the Bicore ASCII data printout using the algorithms provided by the manufacturer. The algorithms used for calculation of respiratory parameters were examined to check they were appropriate. Finally, the values displayed by the Bicore CP100 during ventilation of the lung model were compared to reference values, calculated using data from a Fleisch pneumotachograph (PNT) and Validyne differential pressure transducers with known frequency responses.198

5.3.1.2.1 Assessment of flow measuring apparatus

The effective dead space was taken as the increase in dead space resulting from the insertion of the flow transducer alone or in combination with the occlusion valve between a Portex 15 mm tracheal tube connector and 15 mm Portex right angled connector, as measured by water displacement. The accuracy of the flow transducer was evaluated under three conditions; first connected to a 13 cm 3.5 mm Portex tracheal tube with 15 mm connector attached to a Portex right angled connector, second with a 13 cm 3.0 mm Portex tracheal tube with the same connections and finally with a 10 cm length of 15 mm i.d. tubing connected to each side of the flow transducer. Flows of air from 0 to 500 mL·s⁻¹ were passed through the flow transducer using calibrated rotameters (KDG 1100, Burgess Hill, Sussex, England). A 1-15 L·min⁻¹ rotameter was used for flows up to and including 200 mL·s⁻¹ and a 4-40 L·min⁻¹ rotameter for flows from 200 to 500 mL·s⁻¹. The rotameters had been calibrated for 15 °C and 760 mmHg. The atmospheric pressure at the time of testing was 746 mmHg and the room temperature was 24 °C, although the temperature of the air coming out of the wall outlets was cooler than this. The equipment was evaluated bidirectionally under all three conditions. The actual flow from the rotameter was compared to the digitised flow of the Bicore CP100, displayed as an ASCII output on a personal computer, using software supplied with the Bicore monitor.

The resistance of the flow transducer was assessed bidirectionally using known flows of air from the calibrated rotameters and measuring the pressure drop across the
apparatus with a Validyne MP45 ±50 cmH₂O pressure transducer. The output of the transducer was digitised at 200 Hz using an Analog Devices A-D converter and data collected on an IBM compatible 386 personal computer using RASP software (Section 3.1.2.3). Calibration was with a water manometer.

The frequency response of the flow transducer alone and attached to the 3.5 mm i.d. tracheal tube was assessed, using the pressure chamber method described by Vallinis et al. Briefly, the apparatus consists of an airtight 81 L rectangular box separated in the middle by an acoustic suspension loudspeaker the membrane of which had been sealed with latex. The test transducer is connected to one chamber and a reference transducer (Validyne MP45 ±7 cmH₂O) is connected to the other with a wide bore connector. With this type of connection, the frequency response of the reference transducer has been shown to be excellent in amplitude and phase to at least 40 Hz. The loudspeaker is driven by a sinusoidal wave form produced by a signal generator (Brookdeal Signal Source Type 471) interfaced to a low frequency power amplifier to generate sinusoidal pressure changes within the box. The volume displaced by the speaker movement is in the order of 700 mL per cycle. The volume of air entering or leaving the chamber through the attached flow transducer is negligible in comparison to the displacement volume, such that there is no distortion of the sinusoidal pressure wave form. The flow through the flow transducer is directly proportional to the pressure within the chamber. The amplifier was adjusted to keep the reference transducer pressure constant, which gave peak flows through the transducer of ≈130 mL·s⁻¹ which was within the manufacturer’s stated working range. The direct current voltage outputs of the test and reference transducers were displayed on the X and Y axes respectively of a memory oscilloscope (Tektronix Model 5223) to produce Lissajous loops. With a frequency of 1 Hz from the signal generator, the gain of the reference transducer was adjusted so that the peak to trough voltage outputs of the test and reference devices were equal. The frequency was then increased by one Hz steps to 10 Hz. The attenuation and phase lag were calculated using previously described methods as shown in Figure 5.3.2.
Figure 5.3.2: Assessment of frequency response

\[ \text{Attenuation} = \left( \frac{b}{c} \right) \quad \text{Phase angle} = \sin^{-1} \left( \frac{a}{b} \right) \]

Calculation of attenuation and phase angle from a Lissajous loop. The signal from the reference transducer (ref.) is plotted on the y axis and that from the transducer being tested (test) on the x axis. From Vallinis et al.\textsuperscript{199}

5.3.1.2.2 Assessment of airway pressure measuring apparatus

The accuracy of the transducer measuring $P_{aw}$ was established by applying known pressures over the range of $-25$ to $+50$ cmH\textsubscript{2}O using a water manometer and comparing these with the Bicore measurement displayed as an ASCII output. The frequency response of the $P_{aw}$ measurement device was assessed in an analogous way to that used for the flow transducer.

5.3.1.2.3 Assessment of oesophageal pressure measuring apparatus

Two balloon designs were assessed, the second being a manufacturer's new release in response to feedback from the assessment of the original balloon. The pressure
volume characteristics of the oesophageal balloon were established according to the technique described by Beardsmore et al.\textsuperscript{22} The balloon was submerged in water to a depth of 5 cmH\textsubscript{2}O to empty it of air. It was then attached to a 1 mL syringe and the balloon was withdrawn from the water. Small (0.05 mL) increments of air were then added and the resulting pressure measured using a Validyne MP45 \pm 2 cmH\textsubscript{2}O transducer previously calibrated with a slanting oil manometer (Poddymeter). The pressure volume characteristics of the balloon were plotted and the region where there was no significant change in pressure (i.e. <0.05 kPa) with change in volume, the "working range of the balloon", identified.

The Bicore CP100 uses automated balloon filling. The balloon is vacuumed prior to being filled by a pump which adds 1 to 5 aliquots of 0.126 mL of air as selected by the user. For each filling level the accuracy of the system was assessed by placing the balloon in a closed container that could be pressurised. The pressure in the chamber was varied between \pm 30 cmH\textsubscript{2}O and measured with a water manometer. This applied pressure was compared to the oesophageal balloon pressure measurement using the Bicore CP100 ASCII data display. The frequency response of the oesophageal balloon was determined as described for the flow transducer.

5.3.1.2.4 Assessment of algorithms and calculation of dynamic respiratory parameters

The algorithms used by the Bicore CP100, as described by the manufacturer, were compared with those in common use for research measurements. An ASCII data print out of flow and airway pressure during mechanical ventilation of an SLE (Specialised Laboratory Equipment Ltd, South Croydon, Surrey, UK) neonatal lung simulator was obtained, and used to calculate the dynamic respiratory parameters displayed by the Bicore, using the formulae provided by the manufacturer. The lung model compliance was set at 3 mL-cmH\textsubscript{2}O\textsuperscript{-1} and resistance at 100 cmH\textsubscript{2}O-L\textsuperscript{-1}	extsuperscript{-s}, an SLE neonatal ventilator set at a respiratory rate of 25 min\textsuperscript{-1} and peak pressure of 20 cmH\textsubscript{2}O was used. The flow transducer was connected directly to the 15 mm port of the lung simulator. The calculated values of a selection of the dynamic respiratory parameters were compared with those displayed by the Bicore CP100 to check that the
algorithms were being applied as stated. Application of algorithms for oesophageal manometry were not assessed as this would have required in vivo data collection.

Figure 5.3.3: Time based volume, flow and pressure plots during IPPV of a neonatal lung model

![Time based volume, flow and pressure plots during IPPV of a neonatal lung model](image)


### 5.3.1.2.5 Assessment of dynamic mechanics measurements

The Bicore CP100 was attached via a 3.0 mm Portex tracheal tube to an SLE neonatal lung simulator, which is based on the ISO (International Standards Organisation) design and consists of an isothermal compliance chamber and linear resistance. The lung model was ventilated, both by hand, using a Portex 15 mm disposable T-piece to generate a near sinusoidal respiratory flow pattern (Figure 5.3.3a) with a rate of 50 and 100 min⁻¹, and with a Siemens Servo 900C ventilator, with similar respiratory frequencies and tidal volumes but a more complex waveform (Figure 5.3.3b). A Fleisch size 0 PNT was attached in series, proximal to the flow transducer of the Bicore CP100, and a pressure port was attached at the tracheal tube connection. Validyne differential pressure transducers were used to measure flow and airway pressure. The PNT was calibrated using known flows of air from calibrated rotameters, and the airway pressure transducer with a water manometer. The unfiltered outputs of the Validyne transducers were digitised at 200 Hz using an Analog Devices A-D convertor and data collected on a personal computer using...
RASP software. Flow was digitally integrated to volume. The Fleisch PNT attached to a 3.0 mm i.d. tracheal tube has been shown to have a flat frequency response to 20 Hz.\textsuperscript{198} $R_n$ and $C_{dyn}$ were calculated using the Mead-Whittenberger analysis adapted for neonates.\textsuperscript{203} The lung model was set to a compliance of 1.0 mL-cmH$_2$O$^{-1}$ ($\approx$ 10 mL-kPa$^{-1}$) and resistance of 200 cmH$_2$O-L$^{-1}$-s ($\approx$ 20 kPa-L$^{-1}$-s). The values for $R_n$ and $C_{dyn}$ given by the Bicore CP100 were compared with those set on the test lung and with those calculated from the data collected using the Fleisch PNT.

**Figure 5.3.4: The static accuracy of the Bicore CP100 flow transducer**

![Graph showing the static accuracy of the Bicore CP100 flow transducer](image)

Known flow plotted against flow measured with the Bicore CP100, for the transducer alone and attached to 3.0 and 3.5 mm i.d. tracheal tubes. The dashed line is the line of identity.

**5.3.1.3 Results**

**5.3.1.3.1 Assessment of the flow measuring apparatus**

The effective dead space of the flow transducer, alone and when connected to the occlusion valve was 1.0 and 1.6 mL respectively. The static accuracy of the flow transducer, alone and attached to 3.0 and 3.5 mm i.d. tracheal tubes, over the range
\( \pm 500 \text{mL} \cdot \text{s}^{-1} \) is shown in Figure 5.3.4. A -ve or +ve sign is used to denote flows applied in the expiratory or inspiratory direction respectively. The accuracy was better for the transducer alone, with measurements within 5% from \(-400\) to \(+450\) \text{mL} \cdot \text{s}^{-1}. Attaching a tracheal tube reduced the range over which 5% accuracy was achieved to \(-200\) to \(+300\) \text{mL} \cdot \text{s}^{-1}.

The pressure drop across the flow transducer at flows of 0 to 500 \text{mL} \cdot \text{s}^{-1}, in both the inspiratory and expiratory directions, were as shown in Figure 5.3.5. The resistance of the flow transducer was 1.5 kPa L\(^{-1}\) s\(^{-1}\) at 100 \text{mL} \cdot \text{s}^{-1} and remained similar across the tested flow range. Attachment of the Bicore disposable occlusion valve caused no significant change in resistance at flows below 200 \text{mL} \cdot \text{s}^{-1}, but had an increasing influence at higher flows (Figure 5.3.5).

**Figure 5.3.5: The resistance to flow of the Bicore CP100**

Steady state pressure drop across the flow transducer alone and attached to the occlusion valve during known inspiratory and expiratory flows.
Modified Bode plots of the frequency response of the flow transducer, where phase shift and attenuation (not as a logarithm) are plotted against the logarithm of frequency, are shown in Figure 5.3.6. This was performed for the transducer alone and when attached to a 3.5 mm i.d. tracheal tube. The frequency response in terms of both attenuation and phase angle was degraded considerably by the addition of the tracheal tube.

Figure 5.3.6: Modified Bode plots of the frequency response of the Bicore CP100 flow transducer alone and with a 3.5 mm tracheal tube
5.3.1.3.2 Assessment of airway pressure measuring apparatus

The measured pressures were within 5% of known pressures over the tested range of -25 to +50 cmH₂O. Modified Bode plots of the frequency response for the pressure transducer are shown in Figure 5.3.7. The frequency response was good to at least 10 Hz and considerably better than for the flow transducer.

**Figure 5.3.7:** Modified Bode plots of the frequency response of the Bicore CP100 airway pressure transducer
5.3.1.3.3 Assessment of oesophageal pressure measuring apparatus

Pressure-volume curves for the original and manufacturer's modified balloons are shown in Figure 5.3.8. The near vertical portions of the curves represent the "working range" of the balloon, which for the original balloon was very limited (0.15 mL), but for the modified balloon was much improved (0.35 mL). The original balloon had poor static accuracy at all filling levels (data not shown). However, frequency response was good to at least 10 Hz. The static accuracy of the modified balloon at each of the 5 computer controlled filling levels is shown in Figure 5.3.9. Filling level 3 produced the best results with static accuracy within 5% over the range -30 to +30 cmH₂O. At level 1 the balloon was so empty that the pressure display of the Bicore remained fixed at -50 cmH₂O across the range of applied pressures. By contrast, at level 5, the balloon was so pressurised that it over-read all applied pressures below +20 cmH₂O.

Figure 5.3.8: Pressure-volume characteristics of the original and modified Bicore CP100 oesophageal balloon
5.3.1.3.4 Assessment of algorithms and calculation of dynamic respiratory parameters

Appropriate algorithms were being used for the calculation of tidal breathing parameters. The dynamic respiratory mechanics measurements were based on the Mead-Whittenberger method of analysis\textsuperscript{14} and the calculation of dynamic lung compliance on multiple linear regression as described by Bhutani.\textsuperscript{34} The parameter $C_{el}/C_{dyn}$ which was also displayed was calculated using an algorithm based on the work of Fisher et al.\textsuperscript{197} Unfortunately it is not clear from the original description how the parameter should be calculated during certain patterns of ventilation. The algorithm used for calculation of occlusion mechanics was not based on the single breath technique as described by LeSoëuf et al.\textsuperscript{103} and failed to allow for intrinsic or extrinsic positive end expiratory pressure.
Table 5.3.1 shows the tidal breathing parameters during mechanical ventilation of the lung model, with an SLE neonatal ventilator. There was good agreement between values displayed by the Bicore CP100 and those calculated by applying the Bicore CP100 algorithms to a print-out of ASCII flow and airway pressure data from the Bicore CP100. Both sets of values represent the mean of 10 breaths.

**Table 5.3.1: A comparison of displayed and calculated respiratory parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bicore CP100 Values</th>
<th>Calculated Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory frequency min⁻¹</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Inspired tidal volume mL</td>
<td>40.4</td>
<td>40.0</td>
</tr>
<tr>
<td>Expired tidal volume mL</td>
<td>39.5</td>
<td>39.7</td>
</tr>
<tr>
<td>% Leak</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Inspiratory time s</td>
<td>0.78</td>
<td>0.78</td>
</tr>
<tr>
<td>Expiratory time s</td>
<td>1.47</td>
<td>1.48</td>
</tr>
<tr>
<td>Mean airway pressure cmH₂O</td>
<td>11.1</td>
<td>11.1</td>
</tr>
<tr>
<td>Peak airway pressure cmH₂O</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Peak inspiratory flow mL·s⁻¹</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Peak expiratory flow mL·s⁻¹</td>
<td>73</td>
<td>73</td>
</tr>
</tbody>
</table>

The calculated values have been obtained by applying the algorithms given by the manufacturer to an ASCII data printout obtained from the Bicore CP100 during ventilation of a lung model. %Leak = inspiratory tidal volume – expiratory tidal volume as a percentage of inspiratory tidal volume.

### 5.3.1.3.5 Assessment of dynamic mechanics measurements

During ventilation of the neonatal lung model with both a simple and complex waveform (Figure 5.3.3), the Bicore CP100 and the Fleisch PNT with Validyne transducers both gave values for $C_{dyn}$ and $R$ within 20% of the set values (Table 5.3.2). However the Bicore CP100 gave values that were always lower than the values obtained with the Fleisch.
Table 5.3.2: Simultaneous values of $C_{dyn}$ and $R$ obtained using the Bicore CP100 and the Fleisch PNT with Validyne transducers during IPPV of a neonatal lung model

<table>
<thead>
<tr>
<th>mode of IPPV</th>
<th>$f_R$ min$^{-1}$</th>
<th>$C_{dyn}$ mL·cmH$_2$O$^{-1}$</th>
<th>$R$ cmH$_2$O·L$^{-1}$·s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bicore</td>
<td>Fleisch</td>
<td>Bicore</td>
</tr>
<tr>
<td>Hand</td>
<td>50</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Servo 900C</td>
<td>50</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Lung model compliance 1.0 mL·cmH$_2$O$^{-1}$ and resistance 200 cmH$_2$O·L$^{-1}$·s. Note that the Bicore CP100 does not use S.I. units.

5.3.1.4 Discussion

Until recently the complexity of the measuring equipment and time consuming nature of the analysis of results have limited the use of infant pulmonary function testing to research establishments with highly trained personnel. During the past 5 years several commercially available systems for automated measurements of infant pulmonary function have become available. These automated monitoring systems are being increasingly used in neonatal intensive care by clinicians with little formal training in the assessment of neonatal pulmonary function. It is important that equipment has adequate characteristics to ensure accurate and reliable results when used for clinical monitoring purposes. However, reliable technical data concerning the accuracy of the equipment under dynamic conditions, when attached to the connector (i.e. tracheal tube) that will be used during clinical use, are rarely available.

Evaluation of new equipment should involve both in vitro and in vivo assessments. This study was designed to develop a protocol for the in vitro evaluation of new commercially available neonatal pulmonary monitors. The Bicore CP100 was selected for the development of this protocol. In vitro assessment allows the rapid identification of hardware and software problems that will preclude satisfactory function of a pulmonary monitor. However in vivo studies are also necessary as the
effect of patient respiratory effort, the interaction of the patient with synchronised forms of respiratory support and the influence of tracheal tube leaks cannot be adequately assessed in the laboratory. In addition, any practical difficulties in connecting and positioning the measuring devices and the extent to which such devices are tolerated by infants, require in vivo assessment. Quality criteria for acceptance of technically satisfactory measurements also have to be developed in the clinical setting. The in vivo assessment of the Bicore CP100 is described in Section 5.3.2.

Measurements of the static accuracy of the flow transducer demonstrate the importance of assessing the transducer bidirectionally and while attached to a tracheal tube. The working range of the flow transducer was considerably reduced by the addition of a tracheal tube, with subsequent underestimation of expiratory flows greater than 200 mL·s⁻¹ and overestimation of inspiratory flows greater than 300 mL·s⁻¹. Although this was considerably less than the manufacturer's stated working range, it is adequate for measurements in intubated and ventilated neonates. In clinical practice, flows up to 500 mL·s⁻¹ would only be expected in patients with tracheal tubes larger than those used in this study. Measurements were not repeated with larger tracheal tubes as the manufacturers were planning the release of a new flow transducer with lower resistance that would be more suitable for larger infants.

The frequency response of the flow transducer was also considerably degraded by the addition of a tracheal tube. The degradation in the performance of the flow meter by the addition of a tracheal tube is not a phenomenon peculiar to the Bicore flow meter. The linearity of both Fleisch type and screen type pneumotachographs like the Bicore variable orifice flow meter, which depend on the measurement of a pressure drop across a resistance, has been shown to be altered by changes to the geometry of any tubing connected to the flow meter, particularly sudden changes in diameter. Such changes can result in turbulence at flows that were previously laminar, and alterations in the velocity profile of the gas, such that a greater or lesser proportion of the faster moving molecules are directed close to the points where the differential pressure is measured. The effects of gas composition, humidity and temperature on the static accuracy of the Bicore transducer were not assessed but could be included in the
protocol. Conversion factors for gases other than air are supplied by the manufacturer. However, as oxygen enriched air is frequently used during IPPV, a correction for $F_{\text{IO}_2}$ would ideally be incorporated with the monitor.

Assessment of the airway pressure measurements showed a static accuracy within 5% and flat frequency response to 10 Hz. This is clearly acceptable and was significantly better than for the flow transducer. The frequency response of the flow and pressure measuring devices will be partly determined by the characteristics of the transducer tubing.\textsuperscript{200,206} Stiff fine bore tubing as used in the Bicore CP100 appears to be satisfactory.

The original version of the Bicore CP100 neonatal oesophageal balloon had a very limited working range. In response to feedback from this study, the manufacturer released a modified version with a larger working range and hence adequate static accuracy. An occlusion test\textsuperscript{28,207} would be necessary to ensure that the balloon was functioning satisfactorily in vivo. Although, in theory, an occlusion test could be performed, it was not possible at the time of assessment to display the oesophageal pressure and airway pressure, either as an X-Y plot or as superimposed time based traces, to ensure that the conditions for accuracy had been met.\textsuperscript{208}

Well described algorithms had been used chosen for calculation of tidal breathing parameters and dynamic respiratory and lung mechanics. The method used for calculating dynamic respiratory mechanics is based on identifying points of zero flow at the transitions between inspiration and expiration, when airway pressure is changing very rapidly (Figure 5.3.3). The Bicore algorithm incorporates linear interpolation of the airway pressure and flow samples at these transitions which should improve accuracy. However, multiple linear regression,\textsuperscript{34} which is not dependent on identifying points of zero flow, may be a better method of calculating dynamic respiratory mechanics during IPPV. The method of calculating mechanics from occlusion data was unusual and inappropriate. It failed to allow for any dynamic elevation of lung volume in spontaneously breathing infants, or to be applicable to ventilated infants receiving synchronised respiratory support.
The assessment of the on-line calculation of tidal breathing parameters showed that the algorithms were being applied as stated by the manufacturer. Other algorithms were not checked as they were under constant review by the manufacturer.

In the assessment of the Bicore CP100 during ventilation of the neonatal lung model of known compliance and resistance, mechanics values within 20% of the set values were obtained, even when a mechanical ventilator was used with a high respiratory frequency and complex waveform. The use of more appropriate algorithms, based on multiple linear regression, may have given better results. Obtaining measurements during ventilation of a lung model was quick and simple and did not require access to ASCII or analog outputs from the monitor. This method of assessment is therefore applicable even to monitors that do not incorporate facilities for accessing digital and analog raw data. Ideally, this part of the protocol should be further developed to include assessment using multiple lung models with a wide range of mechanical properties. This approach would be similar to that used for assessing spirometric equipment for use in adults which involves applying a series of known test waveforms to the spirometer.

5.3.1.5 Conclusions

This study demonstrates the kind of assessments necessary if clinicians, scientists and manufacturers are to work towards establishing improved standards of accuracy for neonatal pulmonary monitors. The response of the manufacturers has resulted in much of the numerical data presented here for illustrative purposes becoming rapidly outdated. There is a contrast between the availability of resources to evaluate the safety and efficacy of medicines compared with medical "devices". A committee of experts that can respond quickly to the needs of manufacturers and scientists in developing standards for the performance and assessment of both the hardware and software incorporated in neonatal pulmonary monitors may be required. In setting standards a balance will be necessary between accuracy, ease of use and cost. It is possible that the level of accuracy required for clinical monitoring to permit optimisation of ventilator therapy, which may be of value to individual infants, is less than that required for research studies involving mechanics measurements. However, the level of accuracy of any given monitor in a wide range of clinical
situations should be known, so that the potential limitations of the results are fully appreciated.
5.3.2 The in vivo assessment of neonatal pulmonary monitors

5.3.2.1 Introduction and aims

In vitro assessment of neonatal pulmonary monitors allows identification of many of the problems that can preclude satisfactory function. However, the effect of patient interaction with the monitor and ease of use in the clinical setting can only be assessed by in vivo studies. The development of criteria for accepting measurements and the defining of clinical indications for the use of such monitors also require in vivo studies.

The aims of this study were to assess;

• the ease of use of the Bicore CP100 neonatal pulmonary monitor by resident medical staff on a neonatal intensive care unit
• whether the monitoring device were well tolerated
• whether routine respiratory mechanics measurements were feasible using the Bicore CP100

The study was undertaken in the Special Care Baby Unit (SCBU) of the Homerton Hospital, London. As the original oesophageal balloon was unsatisfactory for clinical use (Section 5.3.1.3.3) the study was undertaken in two parts;

1) assessment of the continuous monitoring and dynamic and passive respiratory mechanics measurement facilities
2) assessment of the oesophageal balloon after the manufacturer released an improved version

5.3.2.2 Materials and methods

5.3.2.2.1 Subjects

For the first part of the study, measurements were performed in preterm neonates requiring mechanical ventilation and surfactant therapy for respiratory distress syndrome. Twenty infants with a median gestational age of 28 weeks (range 25-33) and median birthweight of 1125 g (range 530-2300 g) were studied. Neonates were ventilated using either a Sechrist (7/20 infants) or a Dräger Babylog 8000 (13/20 infants) ventilator. Both ventilators are continuous flow pressure generators. However, the Babylog allows patient triggered breaths; the infant’s respiratory effort being sensed by a hot wire anemometer that is incorporated into the ventilator circuit.
at the patient connector. Infants ventilated with the Babylog were ventilated using synchronised intermittent mandatory ventilation (SIMV). Muscle relaxants and sedatives were not used.

For the assessment of the oesophageal balloon, measurements were attempted in five preterm infants receiving care on the SCBU. Two were intubated and receiving respiratory support and three were recently extubated.

5.3.2.2 Protocol
All registrars and senior house officers, including locum staff, were instructed in the use of the Bicore CP100 for continuous monitoring of respiratory function, by two research registrars taking part in the study. In addition, written instructions for setting up and using the monitor were provided.

After setting up the monitor, staff checked that the pneumotachograph (PNT) calibration was within 5% by giving several 10 mL “breaths” using a syringe. They then connected the PNT between the infant’s tracheal tube and the ventilator circuit. Measurements were made before surfactant was given and then hourly (±10 minutes) for twelve hours. The PNT was left in situ throughout the measurement period except during surfactant administration (when it was removed), and suctioning (when it was disconnected from the tracheal tube).

The following measurements were made;
- tidal breathing indices and dynamic respiratory mechanics (from ventilated breaths) averaged over 10 breaths
- dynamic respiratory mechanics (from ventilated breaths) measured from user selected breaths where expiration was judged to be passive after inspection of a flow volume loop. Patients receiving SIMV could be temporarily switched to IPPV at a higher rate if no passive breaths were observed. Measurements were only to be made if the measured tracheal tube leak was less than 15%. Gentle cricoid pressure or repositioning of the infant could be used when tracheal tube leaks were greater than 15%.

In addition staff were asked to note any practical difficulties using the equipment. Results were recorded by obtaining print-outs using a Hewlett Packard Thinkjet
printer interfaced with the Bicore monitor.

The use of the occlusion valve was assessed if one of the two research registrars were on duty while the infant was being studied. The valve was inserted between the flow meter and ventilator circuit and passive expiratory mechanics measurements attempted on ventilated breaths.

The Bicore oesophageal balloon was assessed at a later date (when an improved design became available) by research registrars. The ease with which the balloon could be passed and a satisfactory occlusion test obtained were assessed.

5.3.2.3 Results

5.3.2.3.1 Continuous monitoring
The medical staff found the monitor easy to set up. The PNT was simple to insert into the ventilator circuit when used with the Sechrist ventilator. When used with the Dräger ventilator an additional adapter was required, making the apparatus more bulky and increasing dead space. The PNT was well tolerated by the babies and there were no complaints from the nursing staff. No PNT had to be removed before the study was complete.

A total of 230 measurements of tidal breathing indices and dynamic mechanics on unselected ventilator breaths were made in 20 subjects, out of a possible 254 measurements (one baby was extubated before the 12 hour study period was completed). Four sets of results were lost as a result of printer malfunction.

The tidal breathing measurements showed that the babies had variable and often large leaks around the tracheal tubes. In only 3 subjects was the measured leak less than 15% for all the tidal breathing measurements. 10 subjects had one or more measurement of tracheal tube leak that exceeded 25%.

5.3.2.3.2 Dynamic mechanics from user selected breaths
All subjects had at least one measurement of dynamic respiratory mechanics made from breaths selected after inspection of individual flow volume curves. The main reason given by the registrars for not recording more measurements were the lack of flow volume curves in which the expiration appeared passive and the consequent
large amount of time required to capture passive breaths. Tracheal tube leak was also a problem. The loops that were accepted by the medical staff were of very variable quality. The registrars complained that it seldom possible to capture and print 3 satisfactory loops in less than 10 minutes. Examples of a good quality flow-volume loop and loops illustrating patient effort and artifact due to water in the ventilator tubing are given in Figure 5.3.10.

Figure 5.3.10: Examples of Bicore CP100 flow-volume loops

5.3.2.3.3 Passive mechanics

The occlusion valve for the measurement of passive respiratory mechanics was assessed in five of the infants. There were no problems inserting the valve in the ventilator circuit. Measurements were attempted on ventilator breaths only. Again patient effort and tracheal tube leak made obtaining a satisfactory number of occlusions to allow reporting of a reproducible results in the small population studied impossible. Satisfactory and unsatisfactory occlusions are shown in Figure 5.3.11.

Figure 5.3.11: Passive mechanics with the Bicore CP100

a) Satisfactory airway occlusion consistent with no patient effort. b) Patient effort during expiration which would invalidate measurements.
5.3.2.3.4 Oesophageal manometry

The oesophageal balloon was assessed for ease of use by 3 research workers all with experience of passing nasogastric tubes and the Dräger catheter tipped transducer (Section 5.4). All considered the balloon was large and stiff for passing either orally or nasally and that the infants took longer to settle after the balloon was inserted than was usual after positioning the Dräger catheter tipped transducer (Section 5.4). After the balloon had been passed into the oesophagus it was found that the highest available balloon filling level was always required to obtain a signal. The positioning of the balloon in the oesophagus was critical to obtaining a satisfactory signal. An occlusion test was attempted in all infants by manually occluding the airway during spontaneous breaths. It was impossible to calculate an accurate ratio of oesophageal to airway opening pressure changes due to the small size of the displayed signals and the lack of any facility to manipulate the data. However, the $\Delta P_{oes} : \Delta P_{aw}$ ratio usually appeared considerably less than 1.0. Examples of the signals during an occlusion test and a period of tidal breathing are illustrated in Figure 5.3.12.

Figure 5.3.12: An occlusion test with the Bicore CP100 to illustrate the unsatisfactory data display
5.3.2.4 Discussion

The setting up and use of the monitor were readily learnt by resident medical staff. Continuous monitoring of tidal breathing indices was easily achieved and well tolerated by the infants. The bulky connections when used with the Dräger ventilator circuit were not unexpected as the circuit already incorporates a flow meter. In clinical practice one is unlikely to want to use the Bicore for continuous monitoring as the Dräger is able to provide continuous flow, volume and pressure measurements. In theory the addition of an extra resistance between the tracheal tube and the Dräger circuit could alter the trigger sensitivity of the ventilator. This did not appear to be a clinical problem in the infants studied, but may have been apparent if the infants were being weaned from the ventilator or receiving other forms of synchronised respiratory support.

The loss of data due to printer malfunction could have been avoided if it had been possible to retrieve data from the monitor for a period of time after data collection. The lack of a facility to display previous data and plot trends is a significant limitation for clinical monitoring purposes.

The data obtained suggest that in clinical practice significant leakage of gas occurs around the tracheal tube. This will invalidate continuous measurements of respiratory mechanics in many infants.

The monitor displays dynamic respiratory mechanics measured and averaged over the preceding ten ventilator breaths. These values can only be of any value if ventilation is passive i.e. there is no respiratory effort from the infant. As is common practice in SCBUs the infants were unparalysed and many were ventilated using SIMV. These babies may have had a mixture of triggered ventilator breaths during which there must have been some patient effort and untriggered ventilator breaths during which respiratory effort may or may not have occurred. The Bicore algorithms result in triggered and untriggered both being classed as ventilator breaths and pooled for the calculation of respiratory mechanics.

The Bicore monitor allows respiratory mechanics to be measured from individual breaths selected by the user after inspection of a flow volume curve. In theory this
allows the user to select passive breaths. The procedure for selecting and inspecting the breaths made this a slow process. Each breath had to be frozen on the screen, inspected and analysed or cleared before another breath could be inspected. The process could have been made quicker by allowing the user to examine a run of breaths selected after inspection of a time based trace. The fact so few captured breaths showed a passive flow volume curve means that the values for respiratory mechanics displayed with the tidal breathing data should be viewed as unreliable in unparalysed infants.

In theory, passive respiratory mechanics or dynamic lung mechanics measurements should be a better option than dynamic respiratory mechanics in unsedated, unparalysed infants. The occlusion device for passive mechanics was evaluated in 5 infants. Patient effort proved to be a problem necessitating multiple attempts at each measurement. The time and patience required to obtain measurements would preclude routine use. In addition there were anxieties about the algorithms used and even if this problem had been addressed the fact that expiration occurs into a continuous flow ventilator circuit invalidates the assumptions underlying the single breath technique (Section 3.2.3.3).

Dynamic lung mechanics measurements should be valid whether or not the infants are making respiratory efforts. However, the Bicore oesophageal balloon proved difficult to pass and a satisfactory occlusion test was not possible. Further improvements to the oesophageal balloon and software would be required before the place of dynamic lung mechanics measurements could be assessed.

5.3.2.5 Conclusions
The in vivo assessment of the Bicore monitor showed that continuous monitoring of tidal volumes, airway pressure and respiratory timing were feasible in unparalysed ventilated preterm infants. Patient effort and tracheal tube leaks made rapid reliable measurements of dynamic respiratory mechanics impossible in this patient population. The same factors remained a problem when passive mechanics measurements were attempted. In theory the use of oesophageal manometry could overcome the problem of patient effort but leaks around the tracheal tube would
remain a problem and the technique is relatively invasive. The oesophageal balloon and software available with the Bicore were not satisfactory for clinical use.
5.4 An assessment of the Dräger transducer tipped catheter for the measurement of dynamic lung mechanics

5.4.1 Introduction and aims

The measurement of transpulmonary pressure, i.e. the difference between pressure at the airway opening and pleural pressure, is necessary for the calculation of dynamic lung mechanics. Pleural pressure ($P_{pl}$) is usually measured indirectly as oesophageal pressure ($P_{oes}$). Three methods of measuring $P_{oes}$ in infants have been described: oesophageal balloon manometry, fluid filled catheter manometry, and micro-manometry. Oesophageal balloons and fluid filled catheters have both been used successfully in healthy infants but there have been problems when these techniques have been applied in small, sick infants. Attempts in the 1980s to use a catheter tip pressure transducer proved disappointing. The device tended to over-read when in situ and did not have any advantage with regard to its size when compared to oesophageal balloons and fluid filled catheters. These problems along with the development of the occlusion techniques for the measurement of respiratory mechanics have resulted in a decline in the popularity of oesophageal manometry.

However, dynamic pulmonary mechanics measurements still retain several potential advantages over the occlusion techniques. Fewer assumptions are involved, they permit measurements throughout the respiratory cycle, involve less apparatus dead space and allow more rapid assessment of lung mechanics once a valid occlusion test has been obtained.

This section describes the evaluation of a new catheter tipped transducer, the Dräger MTC®, for the measurement of oesophageal pressure and pulmonary mechanics in neonates and infants including a group of sick intubated preterm neonates.

The aims of the evaluation were;

- to assess the static accuracy and frequency response of the Dräger MTC®
- to assess the feasibility of using the Dräger MTC® in neonates and infants by determining the success rate for achieving a valid occlusion test and obtaining pulmonary mechanics measurements
Figure 5.4.1: The Dräger 3 French gauge MTC® catheter tipped transducer

a): The 3 French gauge MTC® alone and b): with a 5 French gauge neonatal feeding tube.
All in vitro work was undertaken at The Institute of Child Health, London. Data for the in vivo assessments were collected at The Homerton Hospital, London and The Children’s Hospital, Hannover, Germany.

5.4.2 Assessment of static accuracy and frequency response

5.4.2.1 Materials and methods

The catheter tipped pressure transducer used in this study (MTC®, Dräger Medical Electronics, Netherlands) comprises a sensor containing a silicon pressure-sensitive chip mounted on an extremely flexible 3 French gauge (FG) plastic catheter (Figure 5.4.1). The pressure transducer was originally designed for invasive monitoring in cardiology, urology and neurology. The transducer is sterilised by soaking in activated gluteraldehyde solution for at least 90 minutes followed by rinsing.

The manufacturer states a pressure range of -40 to +40 kPa with a maximum linearity error of 0.5%. The frequency response stated by the manufacturer is more than adequate for lung function testing in even the fastest breathing preterm neonate (-3dB=100 kHz i.e. attenuation is 0.707 at 100 kHz, see Section 3.1.1.1.4). The original output signal (±2mV) was amplified to ±5V using amplifiers built by the engineering departments of Great Ormond Street Hospital, London and The Children’s Hospital, Hannover. For the in vivo assessment of static accuracy, the analog output of the amplifier was digitised at 100 Hz using a RTI 815 A-D convertor and the signals displayed and analysed using an IBM compatible PC and RASP software (Section 3.1.2.3).

5.4.2.1.1 Static accuracy

When not in use the MTC® was stored in its protective plastic tube which also served as a calibration chamber. The MTC® was pre-wetted, for at least 1 hour prior to use by submerging it in sterile water, as recommended by the manufacturer to reduce drift during the calibration and measurement. Preliminary studies had revealed instability of the zero if the transducer membrane was only moistened for a short period prior to measurements.

The linearity of the MTC® with amplifier was assessed over the range -2.946 to +2.946 kPa (-30 to +30 cmH₂O). The MTC® and a Validyne MP45 ±5kPa
differential pressure transducer were calibrated simultaneously using two known signals, 0 and +1.964 (20 cmH₂O) pressure. A water filled manometer was used to generate the latter reference signal. A series of pressures in approximately 0.5 kPa increments from −2.946 to +2.946 kPa were then applied, the exact applied pressure being measured using the Validyne pressure transducer.

5.4.2.1.2 Frequency response

The frequency response in terms of attenuation and phase lag of the MTC® used in conjunction with the amplifier was assessed using the methods described in Section 5.3.1.2.1. The same methods were used to assess the phase relationship of the MTC® and a Hans Rudolph 0-10 L·min⁻¹ pneumotachograph, alone and attached to a 2.5 mm i.d. tracheal tube, with a Furness ±0.2 kPa differential pressure transducer, as used for the in vivo measurements.

Figure 5.4.2: Static accuracy of the MTC® over the range ±2.946 kPa
5.4.2.2 Results

5.4.2.2.1 Static accuracy

Figure 5.4.2 shows the applied pressure against the pressure measured with the MTC® over the range -2.946 to +2.946 kPa. Measurements were accurate within 2%.

5.4.2.2.2 Frequency response

The frequency response of the MTC® with amplifier was satisfactory to at least 10 Hz. At 10 Hz the attenuation was 0.94 (Figure 5.4.3) and there was no measurable phase lag. Assessment of the phase relationship of the MTC® and the Hans Rudolph PNT with Furness pressure transducer showed that the PNT signal lagged slightly behind the MTC® signal when signals between 1 and 5 Hz were applied (Figure 5.4.4). The addition of a tracheal tube produced no further phase lag.

5.4.3 The in vivo assessment of the MTC®

5.4.3.1 Materials and methods

5.4.3.1.1 Subjects

The MTC® was assessed on 51 occasions in 47 spontaneously breathing infants and small children aged 1 day to 24 months, including 9 healthy neonates, and in 18 intubated infants receiving respiratory support aged 1 day to 3 months. Details of the infants are given in Table 5.4.1. With the exception of the 9 healthy neonates, the infants had a variety of cardiorespiratory diseases including respiratory distress syndrome, chronic lung disease of prematurity and interstitial lung disease. The intubated infants were all receiving synchronised intermittent mandatory ventilation using either a Dräger Babylog 8000 or a Hoyer Infant Star Ventilator. The infants were breathing between the mandatory breaths. The measurements were made during short periods disconnected from the ventilator or short periods of continuous positive pressure (for infants measured in London and Hannover respectively).

All measurements on infants with cardiorespiratory diseases were conducted as part of a clinical assessment at the request of the attending paediatrician. Healthy infants were recruited from the maternity wards and informed consent was obtained from a parent.
Figure 5.4.3: Frequency response of the MTC® and amplifier

![Graph showing frequency response]

Figure 5.4.4: The phase relationship of the MTC® and a Hans Rudolph pneumotachograph showing the PNT lags slightly behind

![Graph showing phase relationship]

Phase lag degrees

230
Table 5.4.1: Subject details

<table>
<thead>
<tr>
<th></th>
<th>unintubated infants (n=47)</th>
<th>intubated infants (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median range</td>
<td>median range</td>
</tr>
<tr>
<td>Weight kg</td>
<td>2.60 1.35-12.00</td>
<td>1.15 0.60-4.00</td>
</tr>
<tr>
<td>Length cm</td>
<td>47 34-84</td>
<td>37 29-60</td>
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<tr>
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</tr>
<tr>
<td>Age weeks</td>
<td>7.5 0.1-104</td>
<td>1.2 0.1-12.8</td>
</tr>
</tbody>
</table>

5.4.3.1.2 Measurement methods

Oesophageal pressure was measured using the MTC® which was calibrated using a water filled manometer and 0 and +1.964 kPa pressure signals. The calibration was checked at the end of each study by applying known signals (0 and +1.964 kPa measured with a water filled manometer).

Flow was measured using a Hans Rudolph pneumotachograph (0-10 or 0-30 L·min⁻¹ depending on the size of the infant) and differential pressure transducer (Furness ±0.2 kPa or SensorTechnics 144SC in London and Hannover respectively). The PNT was attached to a Rendell-Baker Soucek face mask in unintubated infants and positioned between the tracheal tube connector and the ventilator circuit in intubated infants. The PNTs were calibrated before the studies using known flows and the calibration checked at the end of each study.

Pressure at the airway opening was measured from a port on the patient side of the PNT when using the smaller PNT or from a port between the PNT and face mask when using the larger PNT. A Furness ±5kPa and a SensorTechnics 144SC pressure transducer were used for measurements in London and Hannover respectively. Calibration of the pressure transducer and the MTC® was performed simultaneously using a water filled manometer and 0 and +1.964 kPa signals.

All analog signals were digitised at 100 or 200 Hz using an Analog Devices RTI 815 A-D convertor. The digitised signals were displayed and recorded using IBM compatible PCs. RASP software or software written by the hospital’s computer.
department were used in London and Hannover respectively. Flow was integrated digitally to give volume.

Occlusion tests were performed in the unintubated infants by manually occluding the PNT at end inspiration for 2 to 3 respiratory efforts. In the intubated infants a Servo (Siemens Elema, Sweden) silicone pinch valve was inserted between the PNT and ventilator circuit and clamped at end inspiration for 2 to 3 respiratory efforts. The valve was removed between occlusion tests to minimise dead space. For some very small infants the combined apparatus dead space (3.2 mL) including the valve was considered to be excessive and in these subjects occlusion tests were performed manually during a brief period disconnected from the ventilator circuit.

**Figure 5.4.5: Occlusion test**

![Time based trace of flow, volume, pressure at the airway opening and oesophageal pressure during an airway occlusion](image)

Time based trace of flow, volume, pressure at the airway opening and oesophageal pressure during an airway occlusion. Note no flow during the occlusion and equal $P_{ao}$ and $P_{oes}$ pressure changes.

**5.4.3.1.3 Protocol**

The measurements were performed during natural sleep in all healthy neonates. No additional sedation was given to the intubated infants. The other infants who were being studied as part of a clinical lung function assessment, which included whole body plethysmography, were sedated with choral hydrate 60 to 80 mg·kg$^{-1}$. 

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The calibrated MTC® was passed through the nose into the stomach as shown by positive pressure swings during inspiration. The MTC® was then withdrawn into the oesophagus as shown by a downward deflection of the pressure signal during inspiration. The MTC® position was then adjusted, as necessary, to achieve a maximal swing with minimum cardiac artefact. It was originally intended to pass the catheter orally but preliminary studies showed this to be impracticable due to the extreme flexibility of the catheter.

With the MTC® positioned, the face mask and PNT were positioned over the infant’s mouth and nose using silicone putty to obtain an airtight seal in the unintubated infants. In the ventilated infants, the PNT, with or without a silicone pinch valve for subsequent airway occlusions, was connected between the tracheal tube and ventilator circuit. If necessary gentle cricoid pressure was used to eliminate a leak around the tracheal tube.

All data for analysis were collected during periods of quiet sleep as assessed by behavioural criteria. With the head in the neutral position an occlusion test was performed. If necessary the catheter position was adjusted to obtain a valid occlusion test \((\Delta P_{\text{s}}:\Delta P_{\text{es}} \text{ ratio } 0.95-1.05)\). An epoch (36-72 s depending on sampling frequency) of spontaneous unoccluded regular breathing was then recorded. This procedure was repeated at least 3 times if the infant remained in quiet sleep.

All infants were continuously monitored during the studies with a pulse oximeter. In addition transcutaneous carbon dioxide and oxygen monitoring were used in most intubated infants.

5.4.3.1.4 Data analysis

Occlusion test data were analysed by calculating the \(\Delta P_{\text{s}}:\Delta P_{\text{es}}\) ratio during each occlusion. The values used were taken from the computer display after the placement of cursors on a time based trace of flow, \(P_{\text{s}}\) and \(P_{\text{es}}\). The flow signal was inspected to allow exclusion of any data showing a leak during airway occlusion. The mean of between 1 and 5 occlusions was calculated for each infant. See Figure 5.4.5.

Data were transferred in ASCII format to Anadat™ 5.2 software which was used to
calculate transpulmonary pressure and dynamic pulmonary mechanics (Section 3.2.2). The program uses multiple linear regression based on a single compartment model. A minimum of 8 regular breaths were used. Only results with a coefficient of variation ($r^2$) of $\geq 0.95$ are reported.

5.4.3.2 Results of in vivo studies

The catheter was easy to pass in all infants even the smallest preterm neonates and those in natural sleep. Following positioning it was well tolerated with very few episodes of oesophageal spasm being observed. Minimal repositioning of the catheter was necessary to achieve a valid occlusion test in most infants.

Checks of the calibration of the MTC® after each study showed an applied pressure change of 1.964 kPa (20 cmH$_2$O) was measured as a mean (range) of 1.966 (1.87 to 2.03) kPa (i.e. within 5%). However, the zero had drifted by up to 0.65 kPa. The median (range) time between calibration and the post measurement check was 170 (62-407) minutes.

For the unintubated infants the $\Delta P_{\text{oes}}:\Delta P_{\text{so}}$ ratio ranged from 0.94 to 1.09, mean (SD) 1.01 (0.03). $\Delta P_{\text{oes}}:\Delta P_{\text{so}}$ was just outside the range of 0.95-1.05 in 7 infants including a healthy preterm neonate. In the absence of a leak around the tracheal tube, the $\Delta P_{\text{oes}}:\Delta P_{\text{so}}$ ratio ranged from 0.98 to 1.06, mean (SD) 1.00 (0.02) in the intubated infants, with only one infant having a ratio greater than 1.05. Changes in oesophageal versus pressure at the airway opening during an airway occlusion are shown for each subject in Figure 5.4.6.

Values for dynamic compliance and resistance for each infant are plotted against weight in Figures 5.4.7 and 5.4.8 respectively. Despite a valid occlusion test an $r^2$ value $\geq 0.95$ (for the multiple linear regression analysis of mechanics) was not obtained in 6 of the unintubated and one of the intubated infants. Figure 5.4.9 shows a recording from one of the these infants. Median $C_{\text{L,dyn}} \cdot \text{kg}^{-1}$ was 6.49 (range 2.80-17.23) mL·kPa$^{-1}·\text{kg}^{-1}$ for the intubated infants and 13.34 (range 4.31-30.6) mL·kPa$^{-1}·\text{kg}^{-1}$ for the unintubated infants. Median $R_L$ was 13.95 (range 4.31-29.16) kPa·L$^{-1}·\text{s}$ for the intubated infants and 7.55 (range 3.19-16.70) kPa·L$^{-1}·\text{s}$ for the unintubated infants.
Figure 5.4.6: Occlusion test data; $\Delta P_{ao}$ plotted against $\Delta P_{oes}$

Occlusion test at end inspiration. $\Delta P_{ao}$ is plotted against $\Delta P_{oes}$ for each infant. The line of identity is shown. a): intubated infants requiring respiratory support, b): unintubated healthy infants and c): unintubated infants with cardiorespiratory disease.
5.4.4 Discussion

The MTC® has a stable, linear calibration in vitro and in vivo, and frequency response characteristics suitable for measuring dynamic pulmonary mechanics in rapidly breathing infants. The zero instability found in the in vivo studies was a little greater than that stated by the manufacturer (0.65 kPa measured, ≤ 0.5 kPa over 16 hours at 37 °C stated). It is possible this is explained by temperature changes, as the MTC® was calibrated at room temperature, but may have been warmer if the calibration was checked soon after removal from the infant. Fortunately dynamic mechanics measurements do not require absolute measurement of $P_{oc}$. A potential problem with the MTC® is the very low voltage output, such that a powerful amplifier is needed in order to use the catheter with a standard ±5 or 10 V A-D
Figure 5.4.8: \( R \) plotted against weight for each infant

\[
\begin{array}{c|c}
\text{Weight kg} & \text{Lung resistance kPa.L\text{-}1.s} \\
\hline
0 & 0 \\
5 & 5 \\
10 & 10 \\
15 & 15 \\
20 & 20 \\
25 & 25 \\
30 & 30 \\
\end{array}
\]

\( \triangle \) intubated
\( \bullet \) healthy
\( \square \) sick

Converter. Despite the addition of a powerful amplifier, the frequency response of the MTC® remained satisfactory to at least 10 Hz, which should be adequate for dynamic mechanics measurements. Assessment of the phase relationship of the MTC® and a Hans Rudolph PNT with Furness pressure transducer showed the PNT lagged slightly behind. This is explained by the need for fine bore connection tubing between the PNT and transducer, and will vary according to the precise characteristics of the flow measuring device and connections used. When using an oesophageal balloon or fluid filled catheter, the presence of catheter tubing between the site of pressure measurement and the transducer is likely to introduce an equivalent delay to that occurring for the flow signal. However the transmission of the signal from the MTC® to the A-D convertor will approach instantaneous. When calculating compliance,
errors of less than 8% occur even when the phase mismatch is approximately 20°. However, larger errors occur when measuring resistance and it has been suggested that flow and pressure measurements should be matched within 1 ms (i.e. 4° at 10 Hz). Introduction of a 1 ms delay in the MTC® signal would have reduced the phase lag between flow and pressure to 4° at 5 Hz with the connectors used in this study. It is planned to modify the software or pneumotachograph, transducer and connecting tubing prior to further data collection.

The success of the MTC® compared with a previously described catheter mounted transducer is likely to reflect its smaller size and improved frequency response.

It was possible to achieve a valid occlusion test in a wide range of infants including intubated very low birth weight neonates with respiratory insufficiency. Placement of the MTC® caused minimal disturbance of the infants such that repeated measurements to evaluate therapeutic interventions seem feasible. The 3 FG catheter, on which the microtransducer is mounted, is much smaller than both standard neonatal feeding tubes and the catheter diameter conventionally used either for mounting an oesophageal balloon or as a fluid filled catheter. This is because the frequency response of the transducer is not influenced by the length and diameter of the catheter. The small size is more appropriate and less disturbing for very small infants.

There are several studies reporting problems in achieving satisfactory occlusion tests when using an oesophageal balloon in small, sick infants. The fluid filled catheter has been applied more successfully in this group. Using a fluid filled catheter, Neto et al obtained valid occlusion tests in 14 spontaneously breathing preterm infants even in the presence of chest wall distortion. The fluid filled catheter has to be flushed at regular intervals to keep the system free of air-bubbles. Although some of the liquid can be withdrawn from the stomach following the measurements, anxieties over fluid overload have prevented some neonatologists from using this technique in small sick infants.

The $\Delta P_{es}:\Delta P_{ao}$ ratio during airway occlusion was between 0.95 and 1.05 in all but 4 of the infants including the intubated infants. The reasons for obtaining a ratio both
greater and less than unity have been described in Section 3.2.1.1.5.

Despite obtaining a valid occlusion test it was not possible to calculate dynamic pulmonary mechanics in 1/18 intubated and 6/51 unintubated infants due to failure to achieve an adequate fit (i.e. \( r^2 \geq 0.95 \)) using multiple linear regression based on an equation for a single compartment lung model. This may in part be due to cardiac artefact (Figure 5.4.9) which may be more apparent on recordings obtained with the catheter tipped transducer due to its greater sensitivity. Potentially this problem could be overcome by breath averaging (ensembling). Another possibility is that the single compartment model may be inappropriate and a more complex model more applicable (Section 6.4.2.2).

Figure 5.4.9: Example of unsatisfactory data for dynamic mechanics with marked cardiac artefact on the \( P_{oes} \) trace (\( r^2 \) value less than 0.95)

![Graph](image)

The calculated mechanics values in these subjects are in accordance with other published data. \( C_{L, dyn} \) values in healthy infants have been found to range from 11 to 20 mL·kPa⁻¹·kg⁻¹ and \( R_t \) may range from approximately 1.0 at one year of age to 10.0 kPa·L⁻¹·s in small preterm infants.²¹²⁻²¹⁵ As expected, infants with cardio-respiratory disease tended to have lower \( C_{L, dyn} \) values and higher \( R_t \) values than healthy infants. The values in intubated preterm infants receiving respiratory support are also comparable to those reported previously.³⁴,²¹⁶ It is possible that this technique
may be suitable for making measurements during respiratory support including patient triggered and intermittent mandatory ventilation if a satisfactory method of validating $P_{res}$ as a reflection of $P_{pl}$ was developed. One such method involving abdominal compression during airway occlusion has been described recently.217

5.4.5 Conclusions

The Dräger 3FG MTC® appears to be a valuable tool for estimating pleural pressure in a wide range of infants and neonates including very small, sick infants. By virtue of its size and the fact that there is no danger of causing fluid overload it may prove to be the best method of measuring dynamic pulmonary mechanics in sick and very young infants. Since problems resulting from inhomogeneous distribution of pleural pressure or failure to equilibrate during an occlusion may occur whichever method is used to estimate pleural pressure, careful validation and interpretation of all measurements remains mandatory.
6. Discussion and future directions

6.1 Introduction
At the inception of this thesis in 1991 there were significant obstacles to the application of infant respiratory function tests for both research and clinical purposes. Major difficulties related to the time consuming nature of the tests, the frequent requirement for sedation and the specialised equipment and training of personnel required. The need to simplify and standardise measurement methods was well recognised. The popularity of dynamic lung mechanics was declining and there was increasing interest in passive respiratory mechanics, partial expiratory flow volume curves and tidal breathing parameters. The use of surface measurements was being advocated to simplify tidal breathing measurements further. In parallel with simplification of methods, technological advances in both measuring equipment and computing were taking place.

The findings presented in this thesis are discussed in the relevant sections. This work along with the findings of others will now be summarised and discussed to address the following issues:

- the limitations of the simpler methods of respiratory function testing
- the contribution and limitations of technical advances to the simplification of infant respiratory function testing
- the choice of respiratory function tests in the research and clinical setting
- the future direction of research in infant respiratory function testing

6.2 Limitations of simpler tests of respiratory function

6.2.1 Tidal breathing parameters
The analysis of tidal breathing parameters as an index of airway obstruction was first proposed in 1981 by Morris and Lane. Several years passed before, in 1988, Martinez et al studied one particular breathing parameter, the ratio of time to peak tidal expiratory flow to total expiratory time ($t_{\text{PEF}}/t_E$), in a cohort of young infants and found that a low value was a predictor of subsequent lower respiratory disease. Potentially this was a very promising finding raising the possibility that infant respiratory function could be assessed during tidal breathing, possibly without
sedation and perhaps with surface measurements. An ideal index of airway function would be highly reproducible with a close relationship to airway resistance. Research conducted for this thesis and recently published findings of others suggest \( t_{\text{PTF}}:t_E \) may not fulfil these criteria.

Section 4.1 examines factors that influence within and between subject variability of \( t_{\text{PTF}}:t_E \), an understanding of which is essential if \( t_{\text{PTF}}:t_E \) measurements are to be used in epidemiological and clinical studies. The factors examined were the influence of sedation, the effect of postnatal age, how many breaths should be analysed and short term within-subject variability. The main conclusions were that \( t_{\text{PTF}}:t_E \) decreases rapidly during the first few weeks of life, that sedation with triclofos sodium has no significant effect on \( t_{\text{PTF}}:t_E \) in healthy infants and that the most representative value of \( t_{\text{PTF}}:t_E \) will probably be obtained by allowing the infant to settle for a few minutes after positioning of the face mask and then recording several epochs of breathing over a few minutes from which 20-50 breaths can be analysed. Although \( t_{\text{PTF}}:t_E \) can be measured with an acceptable level of repeatability in infants from 6 weeks of age, there is large within-subject variability in newborns. Clearly extreme caution should be exercised when using measurements based on small breath numbers during the first weeks of life to predict morbidity in later infancy and childhood.

Section 4.2 examines the relationship between \( t_{\text{PTF}}:t_E \) and airway resistance in both healthy infants and infants with a history of physician diagnosed wheeze. In healthy infants aged 13 weeks or less there was no significant relationship between \( t_{\text{PTF}}:t_E \) and specific airway conductance \( (sG_{sw}) \). In older infants there was a weak relationship between \( t_{\text{PTF}}:t_E \) and \( sG_{sw} \). Both \( t_{\text{PTF}}:t_E \) and \( sG_{sw} \) were significantly lower in wheezy than in healthy infants. One criticism of the study is that the wheezy infants had fairly mild pathology as evidenced by \( sG_{sw} \) values that fell within or only a little below normal values. However for a test to be of use for major epidemiological studies it should ideally be able to detect infants with mild pathology. The subjects in the study described in Section 4.2 were participating in an epidemiological study. A preliminary analysis of this study shows that, as originally suggested by Martinez et al,\(^{127}\) \( t_{\text{PTF}}:t_E \) is lower in the healthy infants who subsequently develop wheeze than in those who do not.\(^{131}\)
By contrast, Adler et al\textsuperscript{218} attempted to reproduce Martinez findings\textsuperscript{127} but found no statistically significant relationship between $t_{\text{PTFE}}:t_{\text{E}}$ measured in the first 10 weeks of life and lower respiratory illness in the first year of life. They also found no significant relationship between $t_{\text{PTFE}}:t_{\text{E}}$ and maximal expiratory flow at functional residual capacity ($V'_{\text{max,FRC}}$) or respiratory resistance ($R_n$). They studied 98 infants which is fewer than Martinez (124 infants) and they give no indication of the power of their study. More recently Yuksel et al have reported that low values of $t_{\text{PTFE}}:t_{\text{E}}$ measured in healthy newborns are associated with wheeze during the first year of life.\textsuperscript{219} However the positive predictive value of a low $t_{\text{PTFE}}:t_{\text{E}}$ was only 41%.

Clarke et al\textsuperscript{220} have also assessed $t_{\text{PTFE}}:t_{\text{E}}$ as a method of detecting mild airway pathology and found it to be less sensitive than $V'_{\text{max,FRC}}$. They found no difference in $t_{\text{PTFE}}:t_{\text{E}}$ between healthy infants, infants with a history of lower respiratory tract infection and infants with asthma. Values outside the 95% confidence intervals for the control group were only seen in a group of infants with severe chronic lung disease of prematurity, most of whom demonstrated flow limitation during tidal breathing. Studies suggest $t_{\text{PTFE}}:t_{\text{E}}$ is a poor method for assessing response to histamine or methacholine challenge.\textsuperscript{221,222}

Clarke et al concluded that $t_{\text{PTFE}}:t_{\text{E}}$ is not a suitable test of infant airway function for most clinical and epidemiological studies, a view supported by the findings presented in Sections 4.1 and 4.2 of this thesis. However Mikkilineni and England\textsuperscript{223} proposed that further research be carried out to evaluate the parameters modulating expiratory flow in health and disease. They reported that in the presence of normal airway resistance, the respiratory muscles play a significant role in altering expiratory flow, however as airway resistance increases $t_{\text{PTFE}}:t_{\text{E}}$ correlates more closely with airway resistance. They suggest that even if $t_{\text{PTFE}}:t_{\text{E}}$ has a limited role in epidemiological studies it could be a useful measure to follow individual children with severe lung disease and to evaluate their response to therapy. In a recent editorial Clarke and Silverman\textsuperscript{224} put forward the suggestion that it may be better to examine $t_{\text{PTFE}}$ and $t_{\text{E}}$ separately since, if respiratory rate increases with the degree of airway obstruction then any shortening of $t_{\text{PTFE}}$ may be masked by a reduction in $t_{\text{E}}$. 

\textsuperscript{243}
In 1992 Stick et al. published a study suggesting the measurement of $t_{\text{PEF-E}}$ could be simplified by using uncalibrated respiratory inductance plethysmography (RIP) instead of a face mask and pneumotachograph (PNT). They subsequently applied the technique in a major epidemiological study examining the effects of in-utero smoke exposure and family history of asthma on respiratory function in the neonatal period. Section 4.3 of this thesis describes a study that attempted to reproduce Stick et al.'s validation findings and extend their work by looking at infants as well as neonates. The level of agreement between $t_{\text{PEF-E}}$ measured with a PNT and RIP is poorer than that reported by Stick et al. The mean difference in $t_{\text{PEF-E}}$ (PNT - RIP) was $-0.14$, 95% limits of agreement $-0.070$, $0.042$. The large discrepancies were mainly accounted for by errors in the measurement of time to peak expiratory flow as there was good agreement between the two methods for the determination of expiratory time (Table 4.3.3). Differences in methodology between the two studies are discussed in detail in Section 4.3.4. One advantage of the data handling software (RASP) used in this thesis is that it enabled storage and detailed examination of the separate RIP ribcage (RC) and abdominal (AB) signals. Examination of these signals revealed that many healthy subjects, while appearing to be clinically "in phase" showed marked variations in the shape of the ribcage and abdominal signals during early expiration (Figure 4.3.4). In these circumstances one would only expect agreement if the RC and AB weighting of the sum signal was correct i.e. if the respitrace was at least qualitatively calibrated. The need to calibrate the respitrace would detract from the simplicity of the method. In view of increasing doubts about the value of $t_{\text{PEF-E}}$ for epidemiological research, further analysis using qualitative calibration was not undertaken.

Respiratory inductance plethysmography provides information about chest wall motion. Chest wall motion in infants is usually considered in terms of a two compartment model, as described by Konno and Mead in which the ribcage and abdomen move independently. In this model, tidal volume measured at the airway represents the sum of the RC and AB volume changes. Inward distortion of either of the compartments during inspiration decreases tidal volume. The very compliant chest wall of the neonate and infant make indrawing of the chest wall during the negative
intrathoracic pressure swings of inspiration more common than in adults. This phenomenon is likely to be greatest if reduced lung compliance or increased airway resistance necessitate the generation of abnormally large intrathoracic pressure swings. Excessive abdominal excursions are then needed to compensate for the inward chest wall motion. This results in asynchronous or paradoxical motion between the RC and AB compartments. Theoretically indices of thoraco-abdominal asynchrony (TAA) may be of value in the non-invasive assessment of respiratory mechanics in infants. Several methods of quantifying TAA are recognised and are summarised in Section 3.5.1.2. In normal adults and infants in quiet sleep, the RC and AB move synchronously. However asynchrony is often observed even in healthy newborns and young infants during active sleep. Considerable care is therefore needed in interpreting results. In addition the rapid reduction in chest wall compliance during the first few months of life is likely to change the sensitivity and specificity of TAA measurements with age. The most likely place for TAA measurements is in paired or serial measurements over a limited time period to assess changes within an infant. Its use is described in monitoring clinical progress and response to therapy in infants with acute upper airway obstruction. In addition changes in TAA have been used to monitor responses to bronchodilators and as a sensitive index of response to bronchial challenge.

6.2.2 Passive respiratory mechanics

Passive respiratory mechanics are measured in spontaneously breathing infants by relating changes in flow or volume to changes in the pressure at the airway opening during periods of muscle relaxation. Relaxation of the respiratory muscles may be invoked by brief airway occlusions at volumes above FRC and this forms the basis of the occlusion techniques. A full theoretical and practical description of the multiple occlusion technique (MOT) for measuring respiratory system compliance ($C_r$) and the single breath technique (SBT) for measuring $C_r$ and respiratory system resistance ($R_n$) is given in Sections 3.2.3 and 3.2.4.

Although the passive mechanics techniques represent a potential advance in that they avoid the problems associated with oesophageal pressure measurements, the occlusion techniques especially the SBT depend on many assumptions. These are
summarised in Table 6.1. Unfortunately these assumptions are least likely to be met in infants with severe airway pathology as;

- equilibration of airway and alveolar pressure will be slow, such that inspiration may occur before equilibrium is reached
- even if equilibrium is reached, post inspiratory or expiratory muscle activity may occur during expiration thereby invalidating a technique which assumes complete muscle relaxation. These problems are likely to be greatest in tachypnoeic infants and in older infants in whom the Hering-Breuer reflex (HBIR) is less strong.
- the respiratory system may not behave as a linear single compartment model, i.e. $C_n$ and/or $R_n$ may vary with lung volume or flow. Examination of pressure-flow loops during measurement of expiratory $R_{aw}$ in infants with airway pathology (Section 4.4) suggest resistance may vary greatly during expiration. This would be expected to produce an alinear SBT flow volume curve, although in practice this was not always the case. This may be because the increased resistance detected using plethysmography is a dynamic phenomenon related to expiratory muscle activity which is absent when $R_n$ is measured. It may also be related to measurements being made at different lung volumes as, following an airway occlusion, infants often inspire before reaching their resting FRC. However it should also be remembered that a linear expiratory flow-volume loop during the SBT is not incompatible with multiple time constants and respiratory muscle activity, or a single time constant due to reciprocal changes in $C_n$ and $R_n$. New methods of analysis utilising more complex models of the respiratory system have been proposed and may potentially overcome some of the problems of measuring infants with lung pathology.

Particular problems related to application of passive respiratory mechanics in intubated and ventilated infants are described in Section 6.4.

The MOT is a technique with fewer assumptions and requiring shorter periods of respiratory muscle relaxation. However for epidemiological and clinical studies, especially outside the early neonatal period, assessment of airway function is usually of much greater interest than assessment of respiratory system compliance. A second method of measuring $C_n$ helps to validate the SBT in individual infants and it has
### Table 6.1: Assumptions of the MOT and SBT methods of measuring respiratory mechanics

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>MOT</th>
<th>SBT</th>
</tr>
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<tbody>
<tr>
<td><strong>Respiratory muscle relaxation</strong></td>
<td>• no activity during airway occlusions</td>
<td>• no activity during airway occlusions</td>
</tr>
<tr>
<td></td>
<td>• no activity during subsequent expiration which lasts sufficiently long for expiration to near FRC</td>
<td>• no activity during subsequent expiration which lasts sufficiently long for expiration to near FRC</td>
</tr>
<tr>
<td><strong>Equilibration of pressure</strong></td>
<td>• complete equilibration during occlusions</td>
<td>• complete equilibration during occlusions</td>
</tr>
<tr>
<td><strong>Respiratory mechanics</strong></td>
<td>• $C_n$ is a constant independent of lung volume</td>
<td>• $C_n$ is a constant independent of lung volume</td>
</tr>
<tr>
<td></td>
<td>• $R_n$ is a constant throughout expiration (i.e. independent of lung volume and flow)</td>
<td>• $R_n$ is a constant throughout expiration (i.e. independent of lung volume and flow)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td>• expiration occurs to atmospheric pressure i.e. not into ventilator circuit</td>
</tr>
</tbody>
</table>

been suggested that when the SBT is used, $C_n$ should also be assessed using the MOT in order to increase confidence in the reported results.\textsuperscript{158}

Given the many underlying assumptions of the SBT a significant failure rate particularly in infants with airway pathology is to be expected. In the comparison of the single breath technique and airway resistance described in Section 4.4, a failure rate of 12% was found in infants of less than 13 weeks of age, of 22% for healthy infants over 13 weeks of age, and of 25% for infants with a history of wheeze aged
over 13 weeks. The main reasons for failure were alinearity of the flow-volume curve and failure to equilibrate or achieve a relaxed pressure plateau during airway occlusion. Had the airway pathology in the group of infants with a history of wheeze been more severe the failure rate may well have been higher. Springer et al\textsuperscript{164} published a similar comparison of $R_n$ and $R_{sw}$. They studied fewer infants (35) but included infants with laryngomalacia as well as infants with recurrent wheeze. Interestingly they report no failures with the SBT. They used slightly less strict acceptance criteria for data, but found good agreement between SBT and MOT determined $C_n$, suggesting a valid measurement of $R_n$ may have been obtained.

Failures have been reported using the SBT in healthy preterm infants during natural sleep in the first week of life. Gappa et al\textsuperscript{158} reported a 25\% failure rate for MOT and 50\% failure rate for SBT even after infants who did not sleep were excluded. Failure to relax, an unstable end expiratory level (MOT only) and pronounced expiratory braking (SBT only) were the main reasons stated for failure.

An understanding of the relationship between $R_n$ measured with the single breath technique and airway resistance or dynamic respiratory mechanics is necessary if its full research and clinical potential is to be realised. Section 4.4 of this thesis explores the relationship between $R_n$ and $R_{sw}$. Both $R_n$ and end expiratory $R_{sw}$ were significantly higher among infants with prior wheeze than in healthy infants of similar age. However an extremely variable relationship between $R_n$ and $R_{sw}$ was observed within infants including many in whom $R_{sw}$ was higher than $R_n$, which is discussed further in Section 4.4.4.5. Nonetheless $R_n$ measurements may be of value in epidemiological studies although it is possible that assessment using the rapid thoraco-abdominal compression technique will prove to be more appropriate (Section 6.2.3). Springer et al\textsuperscript{164} concluded that $R_n$ gave a good estimate of $R_{sw}$ in normal infants and of early expiratory $R_{sw}$ in wheezy infants and infants with laryngomalacia.

The use of standard errors rather than standard deviations or ranges in their paper masks the very wide differences between the methods seen in individual infants. As in the data presented in Section 4.4, several of Springer’s infants had higher values of $R_{sw}$ than $R_n$. The inclusion of infants with upper airway pathology serves to demonstrate the advantage of plethysmography over all other methods in that it shows
changes throughout the breath assisting in the differentiation of upper from lower airway pathology.

A few studies have looked at the relationship passive and dynamic lung mechanics. $C_n$ was compared with $C_{L,\text{dyn}}$ measured using oesophageal manometry in healthy neonates when the multiple occlusion technique was first introduced by Olinsky et al in 1976 and good agreement found. Similarly, good agreement has been found between $C_n$ measured using the SBT and $C_{L,\text{dyn}}$ in healthy neonates. Gerhardt et al studied 39 preterm infants who had recovered from acute respiratory failure before discharge from hospital and at 1 year of age and compared $C_n$ and $R_n$ using the SBT with dynamic lung mechanics. There was good agreement in younger infants. In infants at 1 year of age $C_n$ was 80% of $C_{L,\text{dyn}}$ and $R_n$ was higher than $R_L$, as would be expected by the inclusion of the chest wall which is very compliant in the preterm neonates, but becomes more rigid with increasing age.

The agreement between passive respiratory mechanics and dynamic mechanics has also been assessed in sick and ventilated infants. Thomson et al reported poor agreement in ventilated newborns which they attributed to unsatisfactory oesophageal manometry as shown by a poor occlusion test. However, Popow and Simbruner found reasonable agreement between $C_n$ and $C_{L,\text{dyn}}$ in 10 unintubated neonates with cardiorespiratory disease despite occlusion tests with unsatisfactory $\Delta P_{\text{es}}/\Delta P_{\text{oes}}$ ratios in several patients. There were methodological problems with Popow and Simbruner’s study which failed to take dynamic elevation of FRC into account.

Kugelman et al in 1995 concluded that passive and dynamic respiratory mechanics in ventilated preterm and term infants were highly correlated although values measured with the passive technique were higher and there was marked within-subject variability between the two approaches. Their study had more serious methodological problems as they used an automated measuring method (Bicore) which has been shown to have both unsatisfactory algorithms and an unsuitable occlusion valve for use in ventilated infants (Section 5.3.1).
6.2.3 Rapid thoraco-abdominal compression techniques

In adults and older children, spirometry during forced expiratory manoeuvres provides a simple and sensitive method of assessing respiratory function. Its sensitivity and specificity depends on expiratory flow being independent of effort at modest transpulmonary pressures. The rapid thoraco-abdominal compression (RTC) technique has been developed as a method of obtaining forced expiratory flow-volume curves in infants. Since 1982, when Taussig et al described the use of an inflatable jacket to achieve rapid thoraco-abdominal compression and forced expiration, partial expiratory flow-volume curves have been increasingly used for the assessment of airway function in both healthy infants and infants with respiratory disease, the most commonly quoted parameter being maximal flow at functional residual capacity (\(V'_{\text{max},\text{FRC}}\)).

The advantages of the RTC techniques are that;

- in contrast to the occlusion techniques for the measurement of \(R_n\) they do not depend on the respiratory system being described by a linear single compartment model
- they are simple compared with whole body plethysmography and non-invasive compared with oesophageal manometry
- they primarily reflect airway calibre upstream of the flow limiting segment i.e. they are far less influenced by upper airways resistance than the other techniques. This is particularly relevant in infants who are preferential nose breathers since nasal resistance may contribute about 50% of total resistance.

The main limitations of the techniques are that;

- reproducibility of measurements of \(V'_{\text{max},\text{FRC}}\) depend on FRC being stable between forced expirations. In infants FRC is dynamically determined (i.e. they inspire before expiration ends passively) and varies with many dynamic events including induced changes in airway size, sleep state and dead space. The lack of reliable volume landmarks to which flows may be referenced may account for the very large within-subject variability of \(V'_{\text{max},\text{FRC}}\), with quoted coefficients of variation ranging from 11-36%.
- there are doubts over whether flow limitation is always achieved during RTC.
This is more likely to be a problem in healthy infants than in those with airway pathology and may contribute to the wide variability of reported values both within and between healthy infants.

The wide within and between subject variability of $V'_{\text{max,FRC}}$ can result in values within the normal range even when the shape of the flow-volume curve is markedly concave suggesting airway obstruction. As a result it has been suggested that the sensitivity of partial expiratory flow-volume curves can be increased by assessing the shape of the curve as well as the magnitude of $V'_{\text{max,FRC}}$.\textsuperscript{112}

In adults, spirometry over the full lung volume range produces useful information that cannot be obtained from use of the tidal volume range alone. Over the past few years there has been interest in obtaining full expiratory flow-volume curves in infants by making measurements from raised lung volumes. Early descriptions involved volume stacking using a one-way valve which allowed inspiration but blocked expiration.\textsuperscript{240}

The advantage of this approach is its simplicity, however its usefulness is limited due to variations in respiratory effort within and between infants. This results in lung volume differing between stacked breaths within an infant and reliable lung volume landmarks not being available to allow comparisons between infants. In addition a rising arterial carbon dioxide tension during the stacking process may result in chemoreceptor activity overriding the HBIR and respiratory muscle activity interfering with jacket pressure transmission. The last five years have seen the development of more promising methods of obtaining raised volume forced expiratory curves that involve inflating the infant's lungs to a given airway pressure using either an external gas source or a pump on the infant side of the flow meter.\textsuperscript{241,242} These techniques allow measurement of forced expired volumes in given times (FEV\textsubscript{t}). In adults 1 second is usually used but shorter times are needed for infants as expiration is usually complete by 1 second in very young infants even in the presence of airway obstruction.

Although raised volume RTC by artificial inflation of the infants lungs is a new methodology and relatively few studies have been reported, it has been established that intra-subject variability of the FEV\textsubscript{t} parameters obtained is usually less than 5%
and therefore lower than that seen with $V'_{\text{max,FRC}}$ derived using the RTC during tidal breathing. In addition FEV$_1$ parameters show better correlation with infant size than $V'_{\text{max,FRC}}$. Early reports suggest that FEV$_1$ parameters are better than $V'_{\text{max,FRC}}$ at distinguishing normals from wheezy infants or infants with cystic fibrosis. Standardising lung volume to a given airway pressure is likely to explain the reduced inter subject and intra subject variability. In addition, at high lung volume the HBIR is stronger and respiratory muscle activity is less likely to interfere with transmission of jacket pressure.

It has now been suggested that expiration to residual volume can be achieved by delivering several large sighing breaths in phase with the infant’s respiratory effort, prior to performing a raised volume RTC. This allows measurement of forced vital capacity (FVC), conventional forced expiratory flows such as flow after 50 or 75% of FVC has been exhaled ($F'_{50\%}$, $F'_{75\%}$) as well as FEV$_1$ parameters. The method can be combined with a lung volume measurement, either by gas dilution or plethysmography or to obtain a full assessment of fractional lung volumes. Although this method has only been evaluated by two centres studying a total of 300 children aged 1 month to 4 years it appears highly reproducible and flow limitation appears to be reached over the entire range of the maximal expiratory flow volume manoeuvre.

6.2.4 Measurements without sedation

Although simple measurements such as tidal breathing parameters and passive respiratory mechanics are possible during natural sleep the study of infants with surgically treated oesophageal atresia (Section 4.5) illustrates the practical problems and low success rate associated with this approach both in the neonatal period and in the first few months of life (Section 4.5.3.2). The data collection times were very prolonged in the neonatal period due to the large amount of time spent in non quiet sleep, and in the older infants due to the limited amount of day time sleep. These problems preclude this approach for large epidemiological studies.

It is generally recommended that measurements are made during quiet sleep either natural or obtained with sedation. However ideally one would like to be able to
assess awake infants, especially for large epidemiological studies. There are a few published studies of measurements in awake neonates and infants from Lodrup et al’s group in Norway.\textsuperscript{246-248} They measured tidal breathing parameters and passive respiratory mechanics in 803 healthy term neonates in the first 9 days of life. Virtually all the measurements were made by one operator. Measurements took between 10 and 30 minutes. Exact criteria for accepting and analysing data are not defined but tidal breathing parameters were calculated from only 4 breaths and passive mechanics from a mean of 4 (range 2-14) curves. Intra-subject variability of all tidal breathing parameters was high despite the operator selecting only 4 breaths. The mean $\bar{t}_{\text{PTFE}}$ (0.32 SD 0.11) was much lower than that reported in this thesis for groups of healthy neonates (0.49 (SD 0.11) in Section 4.1 and 0.45 (SD 0.13) in Section 4.3). Stick et al\textsuperscript{122} have reported similar values (mean $\bar{t}_{\text{PTFE}}$ 0.42 (SD 0.14)) to those reported in this thesis. The Norwegian group acknowledge that analysis of a larger number of breaths may have been desirable. Section 4.1 examines the effects of using only a few breaths and concludes that because of the large within infant variability the use of such small breath numbers cannot give a true estimate of $\bar{t}_{\text{PTFE}}$.

Respiratory mechanics measurements obtained on the same measurement occasion in these awake neonates also showed large intra subject coefficients of variation (18% for $C_n$ and 23% for $R_n$). The range of values reported was much wider than those usually reported ($R_n$ 0.015-0.448 cmH\textsubscript{2}O mL\textsuperscript{-1}s and $C_n$ 1.04-9.03 mL cmH\textsubscript{2}O\textsuperscript{-1}) for healthy neonates raising some questions about the accuracy of the method. No attempt was made to validate measurements obtained with the passive flow volume curves by comparison with those calculated when using the MOT.\textsuperscript{158} The possibility of making awake measurements in the oesophageal atresia study (Section 4.5) was considered and a few recordings of tidal breathing with RIP only in quiet but awake neonates and infants examined. Measurements in awake neonates and infants using a face mask were not attempted and may not have been acceptable to many of the parents. The respiratory patterns obtained with RIP were so variable that consistent analysis would have been impossible. The findings of Lodrup’s group and the work presented in Section 4.5 suggest that tidal breathing and passive respiratory
mechanics measurements in awake neonates and infants are unlikely to be of value in clinical or epidemiological research unless very large numbers of subjects are studied.

6.3 Technological advances and infant respiratory function testing

6.3.1 Computing and automated infant respiratory function monitors

Research into infant respiratory function testing has benefited greatly from developments in computer technology over the past 10-15 years. Computers have simplified the acquisition, storage and processing of signals from flow and pressure measuring devices. The ability to perform complex mathematical processing of data has allowed the introduction of measuring devices with a non-linear relationship between the input signal and output signal such as hot wire anemometers for the measurement of flow (Section 6.3.2). Computer technology has also facilitated the use of multiple linear regression (MLR) rather than the mathematically simpler but less satisfactory Mead-Whittenberger method of analysis for the determination of dynamic mechanics. This has been particularly useful in sick infants receiving positive pressure ventilation (Section 6.4.2.2).

In addition to facilitating measurements by research workers specialising in the field of infant lung function testing, advances in computing and microprocessor technology have led to the introduction of many automated pulmonary function testing systems, including continuous monitoring systems for use in intensive care. These automated systems are being marketed for clinical and research purposes and increasingly used by clinicians with little formal training in the assessment of lung function (Section 6.4.3).

Advances in computer technology have also been incorporated into infant ventilators. Until recent years, ventilators for use in infants were usually pressure generators with continuous flow circuits to allow spontaneous breaths. Such ventilators usually incorporated proximal airway pressure monitoring but not tidal volume monitoring. Ventilators are now available that exploit microprocessor technology to allow more sophisticated patterns of ventilation including volume controlled and synchronous breaths (e.g. Dräger Babylog, Servo 300 and SLE 2000). Monitoring of flow and volume as well as airway pressure is increasingly common.
with some manufacturers offering software that calculates respiratory mechanics.

With the increasing availability of commercially produced automated infant pulmonary function equipment several serious problems have become apparent that are currently limiting the potential benefit of such systems in a research and clinical setting;

- a lack of technical standards for such monitors
- a poor understanding by users of the underlying principles and assumptions of the measuring methods leading to factors such as patient respiratory effort, the interaction between the patient and the ventilator, and tracheal tube leaks giving rise to unreliable results
- a lack of appropriate reference values with which to interpret results

Manufacturers assessment of equipment prior to marketing is frequently less extensive than might be desired with reliable technical data concerning the accuracy of the equipment under dynamic conditions rarely available. The in vitro assessment of neonatal pulmonary monitors (Section 5.3.1) aimed to examine how these issues could be addressed by developing a laboratory protocol to evaluate the static and dynamic accuracy of neonatal pulmonary monitors, taking the recently introduced Bicore CP100 as an example. Concern about the technical performance of monitors was confirmed, as serious problems with the oesophageal balloon were recognised as well as problems with algorithms for passive respiratory mechanics based on an occlusion technique. The study demonstrates the type of assessment necessary if clinicians, scientists and manufacturers are to work towards establishing improved standards of accuracy for neonatal pulmonary monitors.

Section 5.2: An assessment of the Capnomac Ultima™ for continuous monitoring of respiratory parameters during IPPV in infants and young children, examines a monitor developed specifically for use during anaesthesia. This monitor was developed for use in adults and adapted to extend its capabilities to the monitoring of patients weighing more than 3 kg. The manufacturer's claim that accuracy should be within 6% was not confirmed in the clinical setting chosen for this study. However, it appeared that the monitor, which proved extremely simple to use, would be able to
track changes within an infant. In developing standards it will clearly be important to take into account whether the automated system is to be used for research or clinical monitoring and the population being measured. The potential benefits of tracking changes within an individual infant, especially during IPPV, as well as the need for more accurate measures of pulmonary function to permit research studies in which patient groups are compared, must be considered when establishing standards for automated monitoring systems. Even when a compromise between simplicity and accuracy is acceptable, the technical performance of the equipment should be clearly defined.

Although in vitro assessment of pulmonary function monitors allows rapid identification of hardware or software problems that will preclude satisfactory function, in vivo studies are also necessary as the effect of patient respiratory effort, the interaction of the patient with the ventilator and the effect of tracheal tube leaks cannot be adequately assessed in the laboratory. Section 5.3.2 describes the problems identified when the Bicore CP100 was introduced into use on a special care baby unit. Use of the monitor was readily learnt by resident staff and measurements of tidal breathing indices were easily achieved. Mechanics measurements were not possible in many infants. Most of the problems identified related to the difficulties of measuring intubated infants receiving respiratory support without the use of muscle relaxants and are discussed further in Section 6.4.2.2.

Automated monitors may have inadequate algorithms for eliminating technically unsatisfactory data and the uncritical or inexperienced user with a poor understanding the underlying principles and assumptions may not recognise the problem. Such problems are compounded in many systems by a lack of facility to allow close inspection and exclusion of data before analysis. This is illustrated by a recent publication in which a group of research workers reported occlusion mechanics in ventilated infants obtained using the Bicore CP100. They did not recognise the algorithms were unsatisfactory and were under the mistaken impression that the infants were breathing out to atmospheric pressure when in fact they were exhaling into the ventilator circuit.\textsuperscript{233}
A further problem with some of the current automated pulmonary function systems is that they impose unsatisfactory limits on the number of breaths or respiratory manoeuvres that can be analysed. As a result publications are appearing in which parameters as variable as $t_{PTEF}:t_E^*$ are reported on measurements of as few as 4 breaths.\textsuperscript{246-248} Again collaboration between manufacturers and users is required to address this issue if automated systems are to make a real contribution to research into infant respiratory function.

In conclusion, advances in computer technology have facilitated developments in infant lung function testing in specialist centres and led to the introduction of commercially available automated systems encouraging clinicians with little formal training in infant lung function testing to undertake measurements for both clinical and research purposes. The clinical value of such measurements is largely unproven (Section 6.4.3). The research applications of these systems cannot be realised until their technical limitations are clearly defined and the users obtain sufficient understanding of the underlying measurement methods and assumptions to allow valid interpretation of the data. Automated technology, if shown to be of proven benefit, is likely to be increasingly incorporated into commercially available intensive care ventilators.

6.3.2 Flow measuring devices

In recent years advances in flow measuring devices have in part contributed to the wider availability of infant lung function testing. Standardised connectors that are compatible with the commonly used tracheal tubes and face masks represent a practical advance. Disposable flow meters have also been developed for incorporation into automated monitors (e.g. Bicore CP100 and Capnomac Ultima\textsuperscript{TM}).

The hot wire anemometer\textsuperscript{250} has a calibration that is independent of gas composition and the technology is such that the device is more sensitive at lower flows. At least one commercially available neonatal ventilator incorporates a hot wire anemometer for measurement of flow and volumes.\textsuperscript{249} A study of dynamic respiratory mechanics measured using a hot wire anemometer demonstrated good agreement with passive respiratory mechanics measurements in 15 young infants.\textsuperscript{251} A further possible
development in flow measurement is the ultrasonic flow meter which is also independent of gas composition. Both these developments have been dependent on the advances in computer technology which now allow the use of flow meters with a linear relationships between the input signal and voltage generated.

6.3.3 Oesophageal manometry

Oesophageal balloons are time consuming to produce and their function is critically dependent on their physical characteristics. Potentially catheter tipped transducers represent a practical advance in oesophageal manometry which in combination with advances in computer technology, may lead to the resurgence of dynamic mechanics measurements in the intensive care unit (Section 5.4). The most significant problem identified in the study reported in Section 5.4 of this thesis is that of phase matching a micro-tipped catheter transducer with airway pressure and flow measuring devices. Close matching is required with a suggested maximum phase difference between the transducers of 4 degrees at 10 Hz. The recent development, by commercial manufacturers (e.g. Jaeger Ltd.), of pneumotachographs incorporating solid state pressure transducers may largely solve the problem. These devices eliminate the need for all transducer tubing and consequently they have greatly improved frequency response characteristics.

6.4 Which respiratory function test when?

This section will consider the choice of respiratory function tests for addressing research questions in both the epidemiological and clinical setting. The current place of respiratory function tests in the clinical management of individual infants will then be examined.

6.4.1 Epidemiological studies

Early epidemiological studies mainly examined normal growth and development of the respiratory system. More recent studies have aimed at identifying groups of infants who may be at increased risk of respiratory morbidity and have attempted to explain this by examining the role of environmental (e.g. tobacco smoke exposure) and genetic (e.g. family history of atopy) factors.
Ideal tests of lung function for use in epidemiological studies would have the following features:

- easy, rapid and safe to perform
- acceptable to subjects and parents
- the outcomes measured would have low within-subject variability and be reproducible between laboratories
- the physiological determinants would be well characterised and bear a direct relationship to risk of disease or outcome of interest. As most respiratory disease in infancy involves the airways, measures of airway function are most likely to fulfil this requirement
- applicable outside specialist laboratories
- collection and analysis of the data would be possible without extensive training
- low/modest cost

In adults, measurement of voluntary forced expiratory flow and volume parameters (spirometry) meets all of these criteria and is the gold standard in all large studies of respiratory outcomes. Unfortunately no currently available test of infant lung function comes close to meeting all these criteria. Although the high interrupter technique shows considerable promise\textsuperscript{254} no validated method currently exists that can be satisfactorily applied in awake infants and sedation is usually required which may limit acceptability to parents. As discussed in Sections 6.2.1 and 6.2.2 measurements of tidal breathing parameters and the single breath technique, which are relatively simple to perform and can be applied outside specialist laboratories, have proved disappointing. Assessment of dynamic lung mechanics require oesophageal manometry which is too invasive for use in most epidemiological studies.

At the present time the most promising infant respiratory function tests for epidemiological studies involve the use of the rapid thoraco-abdominal compression (RTC) technique to obtain forced expiratory flow volume curves. Several recent major epidemiological studies\textsuperscript{72,181,255} have used $V'_{\text{max,FRC}}$ as an outcome variable. Raised lung volume techniques appear to enable measurements of the same parameters as are measured during adult spirometry and may supersede techniques that only produce partial expiratory flow volume curves. The RTC techniques may be
combined with measurements of FRC using a gas dilution method. Unfortunately, such tests though simpler than the plethysmographic assessment of airway resistance and FRC still require highly skilled staff and are only possible in specialised laboratories. This limits the number of subjects that it is feasible for any single centre to study.

6.4.2 Clinical research studies

Lung function tests are used for clinical research studies in two main groups of patients;

- unintubated spontaneously breathing infants
- intubated infants, often neonates, receiving respiratory support.

Selection of tests for the two groups will be considered separately.

6.4.2.1 Spontaneously breathing infants

Most clinical research requiring lung function tests in spontaneously breathing unintubated infants involves subjects with diseases that affect airway function. The test requirements are similar to those outlined for epidemiological studies but the methods chosen must also be applicable to infants with significant pathology. As for epidemiological studies, the most satisfactory tests currently available involve the RTC technique to obtain forced expiratory flow volume curves. Again raised lung volume techniques are likely to prove the most satisfactory particularly if combined with measurements of FRC.

FRC can be measured using plethysmography or the less complex gas dilution methods. However gas dilution methods will underestimate FRC in the presence of trapped gas and may therefore be less satisfactory in subjects with very severe pathology. Plethysmography also permits measurement of airway resistance throughout the respiratory cycle which assists in determining the site of obstruction. Therefore it should be considered for studies involving subjects where upper airway as well as lower airway pathology is likely (Section 4.5).

6.4.2.2 Intubated infants

An understanding of the particular difficulties of measuring intubated infants receiving respiratory support is essential for the selection and interpretation of lung
function tests in this group of patients. Special considerations when making measurements in this group of patients are;

- leaks around uncuffed tracheal tubes
- tracheal tubes acting as non-linear resistances in series with the infant’s respiratory system
- alterations in ventilator settings leading to changes in lung volume and respiratory mechanics

Each of these factors and their implications for lung function testing will be considered in more detail.

Volume measurements may be inaccurate in intubated infants because of leaks around the uncuffed tracheal tubes that are widely used in infants and young children. No systematic evaluations have been performed to determine how large a leak can be tolerated before respiratory mechanics measurements are invalidated. Sly et al.\(^{257}\) have suggested that the difference between inspired and expired volume should be no greater than 5%. Gentle cricoid pressure or a throat pack may be used to minimise a leak but may disturb the infant and are only practical for short periods of time. As leaks around tracheal tubes are likely to be greatest at higher airway pressures, expired volumes are likely to be more relevant than inspired volumes when assessing respiratory function during positive pressure ventilation. All techniques using an occlusion test will be unsatisfactory in the presence of a leak around the tracheal tube. This includes dynamic lung mechanics during spontaneous breathing as this requires the use of oesophageal manometry which is only satisfactory if a valid occlusion test can be obtained (Section 3.2.1.1.5).

Tracheal tubes have a non-linear (i.e. flow dependent) resistance and the situation is further complicated by differences between in vivo and in vitro resistance. This is a result of variations in the internal diameter of the tube due to angulation and compression, as well as the presence of intra-luminal secretions.\(^{258}\) The presence of a non-linear resistance in series with the respiratory system invalidates methods of measuring respiratory function that depend on the respiratory system behaving as a linear single compartment model. The problem is greatest with the single breath technique (SBT) where the addition of a tracheal tube should result in the expiratory
limb of the passive flow volume curve being concave to the volume axis. A linear expiratory passive flow volume curve in an intubated infant must imply time constant inhomogeneity, hence there are serious doubts over the use of the SBT in intubated infants. The main application may be in neonatal ICU where the primary pathology is surfactant deficiency and reduced compliance with relatively normal airway function. In addition, the relatively high resistance of tracheal tubes may reduce the sensitivity with which changes in the infant's respiratory or airway resistance can be detected.

During IPPV, respiratory mechanics may vary with changes in tidal volume, respiratory rate and positive end expiratory pressure (PEEP). This is a consequence of the fact that the respiratory system does not behave as a linear single compartment model. The sigmoid shape of the static volume-pressure curve of the respiratory system means that compliance is lower at extremes of lung volume. In health, infants regulate their FRC such that they breathe on the steep portion of the curve. When IPPV is used, FRC is determined by the interaction between the ventilator settings and the mechanical properties of the respiratory system. Changes in tidal volume, respiratory rate and PEEP may alter FRC, such that the infant is being ventilated at a different point on the volume-pressure curve and has a reduced compliance. This problem is more likely in the presence of lung disease when the linear portion of the volume-pressure curve may be shorter than usual and high mean airway pressures may be required to achieve adequate oxygenation. Alterations in lung volume can also alter resistance by affecting airway calibre. Hence the effect of different patterns of ventilation must be considered when interpreting measurements of lung function obtained during IPPV. This is particularly important during serial measurements when changes in the clinical condition of the infant may necessitate changes in ventilator settings. It must be realised that when pressure controlled ventilation is used, changes in respiratory mechanics will result in changes in delivered tidal volume, even when the ventilator settings remain unaltered.

Infants requiring respiratory support suffer from a wide range of pathologies that result in changes in airway resistance and/or lung compliance. Measurement of dynamic mechanics, with data analysis using multiple linear regression (MLR), is
emerging as the most satisfactory method of assessing respiratory function during intensive care. In infants who are receiving IPPV and making no spontaneous respiratory efforts, respiratory mechanics can be determined without the need for oesophageal manometry. However the latter is necessary for the measurement of dynamic lung mechanics in infants breathing spontaneously (Section 3.2.1). The resurgence of dynamic lung mechanics has occurred partly as a result of advances in oesophageal manometry and computer technology that permits rapid analysis using MLR.

The traditional method of analysing dynamic mechanics data described by Mead and Whittenberger assumes that the mechanical behaviour of the lungs can be described by a linear single compartment model (SCM). The calculation of mechanics is based on data from very few points in respiratory cycle i.e. zero flow points and mid tidal volume points (Section 3.2.1.2.1). This technique is less than ideal for ventilated infants as zero flows occurs at times of rapidly changing airway pressure and a SCM is not strictly applicable. In contrast, with MLR, all the data throughout the respiratory cycle can be utilised and, although the data are often analysed in terms of a linear SCM, it is possible to base analysis on more complex models if a linear SCM model is shown to be a poor fit for the data.

Multiple linear regression analysis using more complex models may improve estimates of respiratory mechanics and has been suggested as a method of detecting lung overdistension during IPPV. Kano et al examined the use of a volume dependent single compartment model (VDSCM). They found the contribution of the volume dependent elastance to the total elastance (%E2) to be an index of overdistension. They showed %E2 was uninfluenced by the mode of ventilation (i.e. pressure controlled or volume controlled) and independent of resistance. %E2 was a more sensitive and specific index of lung overdistension than previously proposed indices ($C_{20}/C$) based on the shape of the dynamic inspiratory flow volume curve.

An additional advantage of MLR for the measurement of respiratory mechanics during IPPV is that it produces an indication of changes in lung volume above the
elastic equilibrium volume. A constant term is calculated that has been shown to be a measure of end expiratory alveolar pressure ($P_{A,EE}$). Subtraction of $P_{A,EE}$ from applied PEEP allows the calculation of intrinsic PEEP. However changes in $P_{A,EE}$ cannot detect changes in lung volume due to collapse or recruitment of lung units.

MLR allows separate analysis of inspiratory and expiratory mechanics. It has been suggested that measurements of expiratory respiratory mechanics may be possible in the presence of a leak around the tracheal tube and during triggered ventilation where expiration but not inspiration may be passive. However this approach has not yet been validated.

A significant practical difficulty in measuring mechanics during respiratory support relates to patient effort during mechanical ventilation. This invalidates the measurement of respiratory mechanics in which pressure at the airway opening is assumed to be the “driving pressure” (Sections 3.2.1 and 5.1). Dynamic mechanics are best measured during either periods of spontaneous breathing or periods of continuous mechanical ventilation, a combination of the two modes creating particular problems with data analysis and interpretation. Some authors favour the use of sedation and short acting neuromuscular blocking agents to facilitate measurements. While this approach may be acceptable in critically ill older infants and young children, in neonatal intensive care there is a move towards the use of minimal sedation and synchronised modes of ventilation. It has been suggested that mechanics measurements during spontaneous breaths rather than ventilated breaths may provide more information regarding subtle changes.

Techniques other than dynamic mechanics are less suitable for measurements in the intensive care setting. The single breath technique, even with a slide valve that allows expiration to atmosphere, is relatively unsatisfactory because of the assumption that the respiratory system behaves as a single compartment model. This can never be the case in the presence of a tracheal tube. Static compliance measures using the multiple occlusion technique are possible and are free of the confounding effects of tidal volume or respiratory rate. Static measurements have contributed to the understanding of dynamic mechanics measurements particularly during surfactant therapy.
However the multiple occlusion technique (MOT) is more likely to disturb the infant and is more complex than the measurement of dynamic respiratory mechanics during IPPV. Furthermore, the MOT provides no indication of airway function. Forced expiratory manoeuvres are also possible in intubated infants but have not been widely used. They require complex equipment and are unsafe in the presence of cardiovascular instability. In addition, there is the concern that in some circumstances the tracheal tube may be flow limiting which would invalidate the technique.

There is increasing evidence from animal studies that lung damage during IPPV results from overdistension of lung units ("volutrauma"). Measures of lung volume in addition to mechanics measurements may therefore be desirable for certain clinical research studies. However, whole body plethysmography is rarely practical and although the gas dilution methods using helium, sulphur hexafluoride (SF6) or nitrogen washout have been developed for use in intensive care they remain too complex to be widely used.

### 6.4.3 The place of respiratory function testing in clinical practice

Ideally clinicians would like to use infant pulmonary function testing to address clinical questions related to the diagnosis and management of individual patients with respiratory disease. However, infant pulmonary function testing has not achieved widespread clinical application. This is related to;

- difficulties in testing and expertise required
- a lack of standardised methodologies
- inadequate normative data especially for intubated and ventilated babies
- absence of a critical assessment of the relative sensitivities and specificities of the different tests

During the last few years, the availability of automated testing equipment (Section 6.3.1) has led to the increasing use of respiratory function tests by clinicians particularly in neonatal intensive care units in the USA. There is very limited evidence to suggest which tests should be used when and how clinical management should be influenced by the results. This is in part due to a lack of knowledge regarding the basic physiology of the sick ventilated lung and the relationship
between ventilator settings, lung function and side effects in different pathological states.

It has been suggested that routine pulmonary function testing during mechanical ventilation is desirable for clinical management and likely to benefit the care of individual patients. Other workers have questioned whether routine lung function testing is clinically useful citing problems with the currently available tests including the high within and between subject variability. This limits the potential for monitoring change within infants and the effectiveness of pulmonary function tests as specific diagnostic or prognostic tools.

Research based evidence to support the use of routine pulmonary function testing during intensive care and justify the costs of such monitoring is limited. In a randomised controlled study of ventilated neonates with respiratory distress syndrome, Rosen et al demonstrated that adjusting ventilation according to the results of regular pulmonary function testing using the commercially available PEDS automated system led to an improved outcome in terms of pneumothorax and less severe forms of intra-ventricular haemorrhage. In their study no attempt was made to measure respiratory mechanics, only tidal volume changes were monitored. However, tidal volume would have varied with changes in respiratory mechanics as pressure controlled ventilation was used. To date no other randomised controlled studies have been published. The practical difficulties of measuring intubated and ventilated infants as detailed above (Section 6.4.2.2) are likely to limit use in intensive care. Intelligent use of flow, volume and pressure measurements generated by ventilators may be the best that can be achieved in the majority of infants, with more specialised measures being reserved for research studies.

6.5 Summary and future directions
At the inception of this thesis in 1991, infant respiratory function testing for both clinical and research purposes was becoming increasingly widespread. This was in part driven by the development of commercially available measuring devices. The need to simplify and standardise methods of assessing infant pulmonary function was well recognised. Simpler methods of assessing lung function for use specifically in
infants had been developed; passive respiratory mechanics and the rapid thoraco-abdominal compression techniques. There was considerable interest in the use of the tidal breathing parameter $t_{T_{PEF}:T_E}$ as an index of airway function both for epidemiological and clinical research purposes.

Research over the past five years has led to a better understanding of the limitations of the newer techniques. The underlying assumptions of the passive respiratory mechanics techniques are a severe limitation particularly in sick infants. The rapid thoraco-abdominal compression techniques remain promising and are still undergoing refinement. In contrast to passive respiratory mechanics, the RTC techniques work better in the presence of airway disease than in healthy infants in whom flow limitation may not be reached. Regrettably the RTC techniques are too complex for application outside specialist laboratories and require the infant to be sedated. Even within specialist laboratories, the time consuming nature of the tests limits the number of infants that can be studied in any one centre. The use of $t_{T_{PEF}:T_E}$ as a valid index of airway function for either epidemiological or clinical research purposes is proving to be increasingly doubtful.

Technological advances in recent years have led to the simplification of data collection and analysis in specialist laboratories and partly account for the recent resurgence of interest in dynamic mechanics measurements in the intensive care setting.

During the past five years the application of infant pulmonary function testing in epidemiological and clinical research studies has increased with a rapidly expanding literature. Unfortunately few of the clinical studies have reached definitive conclusions due to inadequate study design, the use of inappropriate tests and poor interpretation of data. The development of automated measurement "carts" many of which are not adequately assessed, and their use by physicians with little understanding of pulmonary function tests, have contributed to the problem. These automated systems also account for the increasing use of infant lung function testing for clinical purposes in intensive care. Evidence to support this practice and justify the expense is still lacking.
Future advances are likely to result from:

- continued attempts to simplify and standardise measurement techniques. In the absence of very simple methods, standardisation is all the more important to facilitate multicentre studies in both epidemiological and clinical research

- multicentre epidemiological studies into the determinants of infant respiratory health

- well designed clinical research studies which improve our understanding of respiratory physiology in disease states, and the effects of treatments, in particular mechanical ventilation, on lung function. Such research needs to address the complex interactions between the respiratory system and the cardiovascular system, particularly in the intensive care setting. Methods of assessing gas mixing and effective pulmonary blood flow are required to understand how treatments such as surfactant, nitric oxide and ECMO work as the general assumption that changes in lung mechanics are linked to changes in gas exchange may not be valid.\(^{250}\)

- attempts to define the clinical role of infant lung function testing in the intensive care setting and to utilise the increasingly sophisticated flow, volume and pressure data that are being produced by the latest neonatal ventilators.

Such advances are only likely to be realised if there is close collaboration between clinicians, posing the relevant questions, scientists, designing the appropriate studies and manufacturers, producing the necessary equipment.
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Publications


Analysis of Tidal Breathing Parameters in Infancy: How Variable is T_{PTFE:TE}?

JANET STOCKS, CAROL A. DEZATEUX, ELIZABETH A. JACKSON, AH-FONG HOO, KATE L. COSTELOE, and ANGIE M. WADE

Portex Anaesthesia, Intensive Care and Respiratory Medicine Unit, and Unit of Epidemiology and Biostatistics, Institute of Child Health, London, United Kingdom, and Department of Neonatal Medicine, Homerton Hospital, London, United Kingdom

During recent years there has been increasing interest in the measurement of tidal breathing parameters, such as the time to reach peak tidal expiratory flow as a proportion of total expiratory time (T_{PTFE:TE}), and their application to population-based studies of the determinants of early respiratory morbidity. However, little is known about factors influencing the within and between-subject variability of these parameters. This study examines the influence of sedation on T_{PTFE:TE}, estimates the optimal number of breaths and breath epochs required to measure T_{PTFE:TE}, and assesses short-term repeatability of this parameter during the first year of life, taking account of age-related differences. Measurements were made in 266 healthy infants and young children (1 d to 19 mo old). Mean (SD) T_{PTFE:TE} fell from 0.49 (0.11) in the first 2 wk of life to 0.34 (0.09) by 5 to 8 wk, remaining similar thereafter. Sedation with triclofos sodium (75 mg/kg) had no significant effect on T_{PTFE:TE}, which was 0.33 (0.10) in 23 unsedated 6-wk-old infants and 0.32 (0.08) in 49 sedated infants of similar age and weight (95% CI for the difference: -0.05, 0.04). At least 10 breaths in each of two separate epochs from each infant were required to provide a representative estimate of T_{PTFE:TE}. The mean (SD) difference between repeat measurements made 5 to 108 min apart was 0.02 (0.08) in 34 infants younger than 6 wk of age (95% limits of agreement: -0.15, 0.18) and -0.01 (0.04) (95% limits of agreement: -0.09, 0.09) in 30 infants 6 wk and older. The wider within-subject variability observed shortly after birth may limit the clinical and epidemiologic applications of T_{PTFE:TE} when measured during the first weeks of life. Stocks J, Dezateux CA, Jackson EA, Hoo A-F, Costeloe KL, Wade AM. Analysis of tidal breathing parameters in infancy: how variable is T_{PTFE:TE}? Am J Respir Crit Care Med 1994;150:1347-54.

During recent years there has been increasing interest in the measurement of tidal breathing parameters, such as the time to reach peak tidal expiratory flow as a proportion of total expiratory time (T_{PTFE:TE}), and their application to population-based studies of the determinants of early respiratory morbidity. However, little is known about factors influencing the within and between-subject variability of these parameters. This study examines the influence of sedation on T_{PTFE:TE}, estimates the optimal number of breaths and breath epochs required to measure T_{PTFE:TE}, and assesses short-term repeatability of this parameter during the first year of life, taking account of age-related differences. Measurements were made in 266 healthy infants and young children (1 d to 19 mo old). Mean (SD) T_{PTFE:TE} fell from 0.49 (0.11) in the first 2 wk of life to 0.34 (0.09) by 5 to 8 wk, remaining similar thereafter. Sedation with triclofos sodium (75 mg/kg) had no significant effect on T_{PTFE:TE}, which was 0.33 (0.10) in 23 unsedated 6-wk-old infants and 0.32 (0.08) in 49 sedated infants of similar age and weight (95% CI for the difference: -0.05, 0.04). At least 10 breaths in each of two separate epochs from each infant were required to provide a representative estimate of T_{PTFE:TE}. The mean (SD) difference between repeat measurements made 5 to 108 min apart was 0.02 (0.08) in 34 infants younger than 6 wk of age (95% limits of agreement: -0.15, 0.18) and -0.01 (0.04) (95% limits of agreement: -0.09, 0.09) in 30 infants 6 wk and older. The wider within-subject variability observed shortly after birth may limit the clinical and epidemiologic applications of T_{PTFE:TE} when measured during the first weeks of life. Stocks J, Dezateux CA, Jackson EA, Hoo A-F, Costeloe KL, Wade AM. Analysis of tidal breathing parameters in infancy: how variable is T_{PTFE:TE}? Am J Respir Crit Care Med 1994;150:1347-54.
were always performed during natural, unmedicated sleep. Measurements in older infants were frequently obtained following sedation with trichloroethylene (75–100 mg/kg, equivalent to 45–60 mg/kg chloral hydrate) given orally. Room temperature was maintained between 22 and 25°C during all measurements using a servo-controlled air conditioning unit. Most infants were studied in the supine position, although some newborns would only settle in the lateral position. Data analysis was confined to periods of behaviorally determined quiet sleep when posture was stable, respiration regular and no eye movements were seen (8).

When the infant was in quiet sleep, a thin ring of therapeutic silicone putty (Carters, Wiltshire, UK) was placed around the infant's nose and mouth. A transparent facemask (Rendell-Baker, Soucek), attached to the pneumotachograph and recording apparatus, was placed over the nose and mouth and the system checked for leaks (9). Data recording commenced once the infant was breathing quietly through the apparatus. Tidal flow and volume were recorded under resting conditions for a minimum of 5 min, with measurements being repeated after a suitable time interval according to the specific protocol.

Calculation of Tidal Breathing Parameters

All data were inspected by the operator before analysis to exclude periods of highly irregular breathing, sighs, or coughs. The software allows the operator to select a number of consecutive breaths to be analyzed using cursors. Up to 70 parameters can be identified for each breath, including false troughs and peaks. Peak expiratory flow was taken as the first sample of the population distribution are at increased risk from subsequent \( \text{T}_{\text{pTEF}} \) on a small number of breaths is unknown, whether to make comparisons between different groups or to classify individuals according to their results. One application has been to determine whether, as a group, those in the lower bound of the population distribution are at increased risk from subsequent breathing patterns (including sighs, hiccups, and the like), the desire to complete more complex lung function tests during the same measurement session, and perhaps most importantly, the time taken for analysis of recorded data. Most researchers have used an unpaired test and the 95% confidence interval (95% CI) for the mean difference between the groups calculated. Similar comparisons were performed for \( \text{VR}, \text{VT}, \text{TE}, \text{and PTEF}. \)

Protocol B: Effects of Postnatal Age

Several recent reports have noted that values of \( \text{T}_{\text{pTEF}} \) are significantly higher in newborn compared with older infants (7, 13). This difference may reflect more marked bradycardia of expiratory flow during the neonatal period in order to maintain a stable lung volume. Although this study was not primarily designed to determine the effect of postnatal age (PNA) on \( \text{T}_{\text{pTEF}} \), estimates of the mean and variability of \( \text{T}_{\text{pTEF}} \) at different postnatal ages throughout infancy were made to enable interpretation of other findings. Using averages, simple and unweighted (14), were used to highlight age-related changes in the mean and SD of \( \text{T}_{\text{pTEF}} \) (calculated from 20–50 breaths in each subject) for the entire group of 266 subjects as well as for term and preterm infants separately.

Protocol C: How Many Breath Should Be Analyzed?

Although recording of tidal breathing is potentially the simplest of infant lung function tests to perform, the number of breaths that can be analyzed may be limited by the length of time an infant tolerates the face mask and pneumotachograph, the duration of quiet sleep, irregularity of breathing patterns (including sighs, hiccups, and the like), the desire to complete more complex lung function tests during the same measurement session, and perhaps most importantly, the time taken for analysis of recorded data. Most researchers have used a paired test and the 95% confidence interval (95% CI) for the mean difference between the groups calculated. Similar comparisons were performed for \( \text{VR}, \text{VT}, \text{TE}, \text{and PTEF}. \)

Chloral hydrate and its related drug trichloroethylene are frequently used to sedate infants undergoing lung function tests. Trichloroethylene is an active metabolite of chloral hydrate (1 g of trichloroethylene is equivalent to 600 mg of chloral hydrate). Although the influence of these sedatives on many parameters of infant lung function has been reported previously (10, 11), their effect on \( \text{T}_{\text{pTEF}} \) is unclear. The aim of this protocol was to determine whether sedation with trichloroethylene in doses normally used for lung function testing has any influence on \( \text{T}_{\text{pTEF}} \) in healthy infants during the first 2 mo of life.

Subjects. Tidal breathing parameters were measured in 72 healthy full-term infants between 6 and 8 wk postnatal age, of whom 22 were studied during natural sleep, the remaining 49 being studied after sedation with trichloroethylene (75 mg/kg). Infants were recruited from two separate studies designed to be comparable with respect to selection criteria, equipment, measurement conditions, and techniques. The naturally sleeping infants had been recruited as part of a study investigating the effects of postnatal age on the Hering-Breuer reflex (12). The sedated infants were undergoing plasmapheresis studies as part of a longitudinal epidemiologic study and had been recruited from the community (unpublished data).

Statistical methods. The mean \( \text{T}_{\text{pTEF}} \) (obtained from a minimum of two epochs, with between 20 and 50 breaths being analyzed for each individual infant) was compared between the sedated and unsedated group using an unpaired \( t \) test and the 95% confidence interval (95% CI) for the mean difference between the groups calculated. Similar comparisons were performed for \( \text{VR}, \text{VT}, \text{TE}, \text{and PTEF}. \)

Protocol A: The Influence of Sedation

Measurements of tidal breathing parameters may be undertaken in naturally sleeping infants, particularly in the first 8 wk of life. However, in older infants or those in whom measurements of lung mechanics or volumes are also performed, sedation is usually required. The potential effects of sedation on \( \text{T}_{\text{pTEF}} \) must therefore be determined before meaningful comparisons of data can be made within or between laboratories or within infants at different ages.

Statistical methods. The mean \( \text{T}_{\text{pTEF}} \) (obtained from a minimum of two epochs, with between 20 and 50 breaths being analyzed for each individual infant) was compared between the sedated and unsedated group using an unpaired \( t \) test and the 95% confidence interval (95% CI) for the mean difference between the groups calculated. Similar comparisons were performed for \( \text{VR}, \text{VT}, \text{TE}, \text{and PTEF}. \)

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made in 55 infants ranging in age from 1 to 82 wk, of whom 34 were sedated and 10 had been delivered prematurely.

Statistical methods. The homogeneity of variance between breaths within individual infants and any tendency for mean values to change with increasing breath number were investigated. The mean and SD of T_{PTEF} were calculated for each infant from all the breaths available for that infant (which ranged from 29 to 60). These "best" estimates were taken to be each infant's "true" mean and SD in subsequent analyses. Differences between the "true" values for each infant and the mean and SD obtained from every breath number between 5 and 29 (the latter being the maximum achieved in every individual) were then calculated.

These within-infant differences were considered in relation to the between-infant differences obtained for the total sample of 266 infants (Protocol B), i.e., an SD between means and between SDs of T_{PTEF} at any given postnatal age of 0.09 and 0.03 respectively.

Protocol D: Should T_{PTEF} Be Recorded from a Single Epoch?

Recordings of tidal flow and volume in infants indicate that marked changes in breathing pattern can occur over short periods of time. Recordings from a 2-day-old full-term infant clearly demonstrate this phenomenon (Figure 1). In this infant, onset of behaviorally determined quiet sleep was accompanied by marked expiratory braking with a mean (SD) value for T_{PTEF} to 0.213 (0.071) (Figure 1b). This finding obviously raises questions regarding how to determine the most representative estimate of T_{PTEF} in any individual infant.

Methods and subjects. To determine whether results calculated from a single epoch are representative of those recorded over successive epochs, T_{PTEF} was calculated in each infant from five separate epochs of breathing spanning at least 5 min during quiet sleep. Ten breaths were analyzed within each epoch and mean T_{PTEF} calculated for that epoch. Five separate epochs of breathing were obtained from 102 infants less than 6 wk old and from 99 infants whose ages ranged between 6 and 81 wk.

Statistical methods. Results were analyzed separately for infants older and younger than 6 wk postnatal age at time of study. For each age group, paired tests were performed on the difference between the first and second epoch within each infant to assess whether there was any bias in readings from the first epoch.

If a single epoch is representative of recordings over successive epochs, then variation within infants between epochs will be small in comparison to that between infants. Random effects models (15) were used to compare the variation between individuals to that between epochs within individuals. 95% CI for the percentage of total variation attributable to differences between epochs were calculated.

Protocol E: Short-term Within-subject Repeatability

Interpretation of the clinical or physiologic significance of differences in T_{PTEF} either between or within individuals with respect to increasing postnatal age or therapeutic interventions is dependent on some knowledge of the repeatability of these measurements under basal conditions. The aim of this protocol was to assess short-term within-subject repeatability of T_{PTEF}.

Subjects. Paired measurements of T_{PTEF} were available from 64 healthy infants (1 d to 62 wk postnatal age), of whom 31 had been delivered prematurely and 26 had been sedated. The second measurement was made a median of 12 min (range 5–108 min) after the first. In each infant, measurement of T_{PTEF} on both occasions was based on 50 breaths collected from several epochs of breathing spanning at least 5 min.

Statistical methods. Differences between the first and second occasions were calculated and the limits of agreement for the difference between the two results determined (16). Results were analyzed for the group as a whole and separately for infants younger and older than 6 wk of age respectively.

RESULTS

Effect of Sedation

Characteristics of the two groups and the results of tidal breathing analyses are summarized in Table 1. There were no significant differences between the groups with respect to sex, birth-weight, gestational age, or age, weight, and length at time of test.

Mean (SD) T_{PTEF} was 0.325 (0.087) in the naturally sleeping infants and 0.322 (0.079) in the sedated infants. The difference between the groups of -0.003 (95% CI: -0.046, 0.040) was not significant (p = 0.89).

Sedation had no significant effect on T_{E} or RR. However, V_{T} and P_{TEF} were slightly greater among sedated than unsedated infants (mean difference: 4.0 ml [95% CI: 1.3, 6.8 ml] and 12.9 ml/s [95% CI: 3.7, 21.9 ml/s], respectively).

Effects of Postnatal Age

Mean T_{PTEF} fell rapidly in both preterm and term infants from 0.49 (0.11) during the first 2 wk of life to 0.34 (0.09) by 5 to 8 wk of age, after which average values leveled off. Within-individual variability (i.e., mean within-subject SD of T_{PTEF}) followed a similar pattern, falling from approximately 0.08 in the first 2 wk of life to 0.05 by 5 wk postnatal age but remaining similar thereafter. There were no apparent differences in between-infant variability for the term and preterm groups, nor did this change with increasing postnatal age. The between-infant standard deviation of T_{PTEF} at
TABLE 1

EFFECT OF SEDATION ON TIDAL BREATHING PARAMETERS

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<td>4.78 (0.71)</td>
<td>0.04 (-0.28, 0.27)</td>
</tr>
<tr>
<td>TpTEF:Te</td>
<td>0.325 (0.097)</td>
<td>0.322 (0.079)</td>
<td>-0.003 (-0.046, 0.043)</td>
</tr>
<tr>
<td>Te, s</td>
<td>0.82 (0.18)</td>
<td>0.78 (0.19)</td>
<td>-0.04 (-0.14, 0.06)</td>
</tr>
<tr>
<td>RR, min⁻¹</td>
<td>42.9 (7.3)</td>
<td>45.8 (9.4)</td>
<td>2.9 (-1.5, 7.4)</td>
</tr>
<tr>
<td>VT, ml</td>
<td>36.1 (4.8)</td>
<td>40.1 (5.6)</td>
<td>4.0 (1.3, 6.8)</td>
</tr>
<tr>
<td>PTEF, m/s</td>
<td>67.7 (14.4)</td>
<td>80.5 (18.8)</td>
<td>12.8 (3.7, 21.9)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: M = male; F = female; BW = birthweight; W = body weight at time of test; TpTEF:Te = time to peak tidal expiratory flow as ratio of total expiratory time; Te = expiratory time; RR = respiratory frequency; VT = tidal volume; PTEF = peak tidal expiratory flow; 95% CI = 95% confidence interval of the mean difference between groups.

How Many Breaths Should Be Analyzed?

Figure 2 shows how quickly (breath-wise) the true means and SD were approached. As a consequence of the increased within-infant SD among infants younger than 6 wk of age, there was a tendency for the younger infants to need more breaths than older infants to approach their "true" mean but less to approach their "true" SD. It can be seen that by 10 breaths, most infants were within 0.09 (i.e., approximately 25%) of their "true" mean and within 0.06 of their "true" SD. By 15 breaths these figures had fallen to 0.06 and 0.04 respectively.

Considered in relation to the variability of TpTEF:Te between subjects (i.e., approximately 0.09 irrespective of age [Protocol B]), these results imply that use of a limited breath number may result in a high proportion of infants being misclassified. For example, the probability of any infant whose "true" TpTEF:Te fell on the 10th centile for his/her age being reported on the 30th centile or above would be 0.13, 0.08, 0.03, and 0.01 when basing the results on 5, 10, 15, and 20 breaths respectively.

Should TpTEF:Te Be Recorded from a Single Epoch?

Table 2 shows the average TpTEF:Te for each epoch, according to age group. There was a tendency for the first readings of TpTEF:Te to be lower. The average rise (2nd - 1st epoch) was similar in both age groups being 0.025 (95% CI: 0.005, 0.054; p = 0.0129) in the younger and 0.026 (0.015, 0.036; p < 0.00005) in the older infants. Apart from the tendency for the first epoch to give a lower reading, there was no other evidence of any consistent time-related changes in TpTEF:Te readings between epochs.

TABLE 2

VARIABILITY OF TpTEF:Te DURING FIVE SUCCESSIVE BREATHING EPOCHS IN HEALTHY INFANTS

<table>
<thead>
<tr>
<th></th>
<th>&lt; 6 wk (n = 102)</th>
<th>&gt; 6 wk (n = 99)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Epoch Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>0.457</td>
<td>0.120</td>
</tr>
<tr>
<td>2nd</td>
<td>0.492</td>
<td>0.123</td>
</tr>
<tr>
<td>3rd</td>
<td>0.512</td>
<td>0.126</td>
</tr>
<tr>
<td>4th</td>
<td>0.516</td>
<td>0.119</td>
</tr>
<tr>
<td>5th</td>
<td>0.499</td>
<td>0.127</td>
</tr>
</tbody>
</table>

any given age was approximately 0.09 for the mean values and 0.03 for its SD.

Figure 2. (a) Absolute differences between mean TpTEF:Te calculated from between 5 and 29 breaths and the "true" mean (based on up to 60 breaths) in each of 55 infants. By 15 breaths mean values were within 0.06 of the "true" mean for most infants. (b) Absolute differences between within-subject SD for TpTEF:Te based on 5 to 29 breaths and the "true" SD in the same 55 infants.

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<td>SD</td>
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</tr>
<tr>
<td>5th</td>
<td>0.499</td>
<td>0.127</td>
</tr>
</tbody>
</table>

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TABLE 3

COMPONENTS OF VARIANCE

<table>
<thead>
<tr>
<th>Total Variation Attributable to Differences between Epochs Within-Infants</th>
<th>&lt; 6 wk</th>
<th></th>
<th></th>
<th>≥ 6 wk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
</tr>
<tr>
<td>All five successive epochs</td>
<td>40.8%</td>
<td>35.7, 46.9</td>
<td>19.7%</td>
<td>17.2, 22.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omitting first epoch</td>
<td>35.6%</td>
<td>30.6, 41.9</td>
<td>17.1%</td>
<td>14.7, 20.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To assess whether the observed alterations in TPEF:Te were associated with increased ventilatory drive, paired t tests were used to assess changes in VT, Te, TPEF:Te, PTEF, and RR between the first and second epochs. Among the younger infants, mean (SD) VT rose from 19 (7) to 20 (8) ml, 95% CI difference (2nd - 1st) being 0.4, 1.3 ml (p < 0.002), accompanied by a small rise in PTEF from 49 (18) to 52 (20) ml/s (95% CI 0.8, 5.1 ml/s, < 0.01), with no significant change in any other parameter. In the older infants, RR, VT, and Te showed no significant changes (p > 0.1), whereas there was a small fall in mean (SD) PTEF from 94 (32) ml/s to 91 (30) ml/s (95% CI -5.6, -0.4 ml/s p = 0.02). This was accompanied by a small rise in TPEF from 0.24 (0.07) s in the first epoch to 0.26 (0.08) s in the second (95% CI 0.01, 0.03 s, p < 0.0001).

Table 3 shows the variance attributable to differences between the five epoch readings as a percentage of the total variation. Among the younger group more of the total variability was due to differences between epochs than for the older infants. This was observed even when the first epoch was omitted from the analysis.

Figure 3. Difference between repeat measurements of TPEF:Te plotted against mean TPEF:Te in 64 healthy infants. The mean difference and 95% limits of agreement (15) are shown.

Short-term Within-subject Repeatability

For the group as a whole, the mean (SD) difference in TPEF:Te (2nd - 1st observation) was 0.006 (0.067). This was not statistically significant (p = 0.49; 95% limits of agreement: -0.127, 0.139) (Figure 3). Although absolute difference tended to increase with increasing mean TPEF:Te, this could be attributed almost entirely to the influence of postnatal age, because the highest values of TPEF:Te were obtained in infants younger than 6 wk of age (Protocol B), in whom these absolute differences were also greater (Figure 4). Results are summarized according to age group in Table 4.

DISCUSSION

Evaluation of tidal expiratory flow patterns as an index of airway obstruction in infants must take account of a number of interrelated factors that may influence such patterns, including the postnatal age of the subject. During passive expiration, the elastic recoil pressure of the respiratory system (Pel) provides the driving force to overcome the flow-resistive pressures of the respiratory system. The higher the Pel and the lower the airways resistance, the higher the flows that will be achieved at any given time. Because Pel is highest at end inspiration (a time when airways are also usually well distended), PTEF should theoretically be observed almost instantaneously at onset of expiration (i.e., TPEF:Te would be extremely low). This pattern is, however, rarely observed except in adults who have been trained to relax or in infants in whom muscle relaxation has been induced by end-inspiratory occlusion (17), demonstrating that some braking of expiratory flow is a nor-

TABLE 4

WITHIN-SUBJECT REPEATABILITY OF TPEF:TE

<table>
<thead>
<tr>
<th>Observation</th>
<th>1st</th>
<th>2nd</th>
<th>Differences (2nd - 1st)</th>
<th>Limits of Agreement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>n</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>All</td>
<td>64</td>
<td>0.366 (0.119)</td>
<td>0.372 (0.139)</td>
<td>0.006 (0.068)</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>34</td>
<td>0.445 (0.094)</td>
<td>0.461 (0.118)</td>
<td>0.016 (0.084)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>30</td>
<td>0.277 (0.073)</td>
<td>0.272 (0.082)</td>
<td>−0.005 (0.042)</td>
</tr>
</tbody>
</table>

* 95% limits of agreement, i.e., 2 SD above and below mean within-subject difference.
mal feature of tidal breathing. It has been suggested that the rapid rise to PTEF observed in adults with airway obstruction may either reflect early onset of flow limitation during tidal breathing or that a progressive reduction in postinspiratory braking of expiratory flow occurs to prevent excessive hyperinflation in the presence of a prolonged time constant (3). A recent report that phasic diaphragmatic activity ceases abruptly at end inspiration in patients with severe chronic airflow obstruction (18) suggests that PTEF probably reflects alterations in the control of breathing in response to underlying mechanics rather than being a direct index of airway size. This relationship is likely to be even more complex in infants especially during the first weeks of life, when expiratory braking mechanisms and vagally mediated stretch receptor reflexes interact to control end-expiratory lung volume and optimize ventilation (19).

Recordings of diaphragmatic and posterior cricoarytenoid activity during tidal breathing have identified four major respiratory patterns in healthy newborn infants during sleep (19). Varying degrees of expiratory braking, which may be predominantly due to laryngeal or postinspiratory diaphragmatic activity, or to a combination of both, commonly alternate with periods of more rapid breathing when modulation of expiratory flow is minimal. The breath to breath variability and brief duration of these different patterns led Kosch and coworkers (19) to suggest that the expression of these patterns was not merely a reflection of changes in sleep state (which was not formally monitored) but rather reflected the immaturity of the newborn's respiratory control system. It was proposed that laryngeal control of expiratory airflow involved reciprocal action between decreased abductor activity (posterior cricoarytenoid) and activation of laryngeal adductors (e.g., thyroarytenoid), and was accompanied by a late onset of peak expiratory flow on release of such braking. This pattern of breathing (which would give rise to prolonged values of PTEF) would maintain an elevated lung volume and optimize gas exchange until near end-expiration while minimizing progressive increases in end-expiratory level. With increasing postnatal age, the need to modulate expiratory flow and timing in order to maintain a stable functional residual capacity (FRC) diminishes.

Effect of Postnatal Age

The rapid fall in both the mean values and within-subject variability of PTEF observed during the first 6 wk of life in this study is consistent with such a pattern of maturation. Values of approximately 0.5 for PTEF at birth are similar to those previously reported in neonates (7) and reflect the marked expiratory braking that is frequently observed during the first weeks of life. Similarly the high within-subject variability among the neonates reflects the wide range of breathing patterns adopted during this period (19). Lower and more reproducible values of PTEF could have been obtained had a limited number of breaths with clearly defined peak flow patterns been selected (Figure 1b). However, in view of our subsequent findings with respect to number of breaths and epochs, this would not have provided representative values for newborn infants.

In this study, all analysis was performed after completion of data collection, data only being rejected according to pre-established exclusion criteria (irregular breathing, sighs, and the like). This approach is far less subject to potential "bias" than automated systems in which the operator can select individual breaths after inspection of results during data collection.

Mean values of PTEF of approximately 0.3, as found in the present study in infants beyond 6 wk of age, are similar to those previously reported in both healthy infants (1) and adults (3). The consistency of these values suggests that expiratory braking to maintain a dynamically elevated lung volume, with the associated prolongation of PTEF, diminishes rapidly beyond the neonatal period. Thus, although any association between airway size and PTEF is likely to be weak or absent during the first weeks of life until a stable FRC is established, beyond this period one might expect this association to be similar to that reported in older children and adults (3–5, 13).

The Effect of Sedation

The marked age-related changes in PTEF during this study are unlikely to be explained by the increased use of sedation among older infants. Large doses of chloral hydrate have been reported to cause upper airway obstruction in susceptible subjects due to a loss of abductor activity (20). Consequently it is possible that administration of triclofos sodium (a derivative of chloral) might alter the pattern of expiratory flow modulation and hence PTEF. However, there was no significant difference in PTEF between the group of naturally sleeping 6-wk-old infants and a group of infants of similar age, weight, and sex who had been sedated with 75 mg/kg of triclofos. The slightly increased VT and PTEF observed in the sedated infants may reflect slightly warmer environmental temperatures (approximately 26°C) during pletysmographic studies than when infants were measured in a cot.

Ideally the influence of sedation should be assessed by paired within-subject studies. However, this is rarely feasible in sufficient numbers to reach meaningful conclusions. Infants were not randomized according to sedation, this choice being based simply on whether they had been recruited for pletysmographic studies or for the simpler measurement of passive mechanics. We confined our comparison to full-term infants between 5 and 8 wk of age since, at this age, simple lung function measurements are feasible without sedation. It is possible that the effect of sedation would be more marked in newborn infants in whom laryngeal braking is more common than in older infants. Because we do not sedate infants during the first month of life, we cannot clarify this issue. However, the results of the current study do indicate that the observed fall in PTEF beyond the neonatal period is unlikely to be due to the increased use of sedation in older infants.

Number of Breaths and Epochs Analyzed

Standardization of the number of breaths and epochs used to estimate PTEF is needed to allow reports from different centers to be compared. We have assessed the influence of breath and epoch number on the estimated mean and variability of PTEF.

Computer-assisted analysis of tidal breathing, such as the system used in this study, allows breath by breath analysis of very large numbers of breaths under direct operator control. However, data in the present study were collected in discrete epochs of 30 to 60 s, thereby limiting the number of consecutive breaths that could be analyzed. Both posterior cricoarytenoid and postinspiratory diaphragmatic activity are known to increase following sighs (18), which occur fairly frequently during quiet sleep. Hence the 10 breaths immediately following a sigh were excluded from analysis, thereby further limiting the number of consecutive breaths that could be obtained in any given individual. Although any periods of marked irregularity suggestive of a change in sleep state, body movements, or hiccups were excluded from analysis, breaths were not selected according to pattern of breathing, since, with computer-assisted analysis, precise timing of peak flow could be identified with greater accuracy than is possible using manual analysis. Thus at least 29 consecutive breaths in each of 55 in-
tions were obtained in order to examine random errors in the esti-
mate of \( T_{PTEF:TE} \) arising from the use of a lesser number of breaths. Published studies (1, 7) have commonly reported \( T_{PTEF:TE} \) as the mean of 10 (or even fewer) breaths. Our results suggest that, while this may be adequate for infants older than 6 wk of age, a closer estimate of the true value is likely to be obtained from 15 to 20 breaths per infant (Figure 2a, b). Given the increased within-subject variability observed in neonates, a minimum of 20 breaths and preferably more should be analyzed at this age, to reduce ran-
don error in the estimate of \( T_{PTEF:TE} \). Martinez and coworkers (1) showed that healthy infants in the lower tercile of the population distribution of \( T_{PTEF:TE} \) when measured at 2 to 3 mo of age, were more likely to develop wheezing during subsequent respira-
ry infections. This relationship was strongest among boys and was thought to reflect the relationship between \( T_{PTEF:TE} \) and di-
minated airway size prior to any respiratory illness (i.e., some con-
genital predisposition). Our findings suggest that results based on a limited number of breaths may result in misclassification of a significant proportion of infants into the wrong terciles. This mis-
classification could result in an underestimate of the strength of any observed associations between \( T_{PTEF:TE} \) and other current \( \text{VT} \) or subsequent respiratory morbidity. However, since within-subject variability decreases with increasing postnatal age (Table 4), the extent to which older infants (i.e., those over 6 wk of age) might be misclassified by basing results on only 10 breaths may be lower than predicted from the current study.

As previously discussed, patterns of breathing exhibit marked variability, especially in newborn infants (19). Hence, estimates of \( T_{PTEF:TE} \) based on a single epoch may not provide a represen-
tative value, even if a large number of breaths have been ana-
yzed. Because it may be difficult to consistently obtain more than 10 consecutive breaths in each infant, the effect of increasing the number of epochs on estimates of \( T_{PTEF:TE} \) was examined using 10 breaths from each of five separate epochs of breathing. More than 40% of the total variation between infants younger than 6 wk of age was explained by variation within infants between epochs, almost double that observed in older infants (Table 3). This again confirms the findings of Kosch with respect to random changes in breathing pattern among young infants.

There was a tendency for \( T_{PTEF:TE} \) to be lower in the first com-
pared to subsequent epochs. This may reflect adaptation by the infant to the increased load imposed following placement of the
ask and recording apparatus (21) with a resulting temporary reduction in the degree of expiratory flow braking. Although it has been suggested that mean values of \( T_{PTEF:TE} \) recorded using in-
ductance plethysmography are similar with or without a mask in situ, breathing does tend to become more regular following place-
ment of a face mask (7). The first epoch was usually, though not invariable, recorded as soon as there was a leak-free seal and behav-
ioral evidence of quiet sleep (i.e., within a couple of minutes of mask placement). It is therefore possible that quiet sleep was less well established during the first compared with subsequent epochs. Although it has been suggested that removal of the face mask every 20 s should be employed to minimize \( CO_2 \) retention, this procedure may in itself cause alterations in sleep state and increase the variability of resting breathing patterns. Although statistically significant changes in \( \text{VT} \) and PTEF did occur between the first and second epochs in the younger infants, these are prob-
bly too small to be of physiologic significance and do not sug-
gest that increasing ventilatory drive was primarily responsible for the observed differences in \( T_{PTEF:TE} \). Among the older infants the rise in \( T_{PTEF:TE} \) appeared to be predominantly attributable to the increase in \( T_{PTEF:TE} \) which occurred in the absence of any as-
sociated change in \( T_e \).

Apart from the tendency for first readings of \( T_{PTEF:TE} \) to be lower, there was no other evidence of any consistent time-related changes in \( T_{PTEF:TE} \) readings between epochs. Recording of a larger number of consecutive breaths in each epoch for all sub-
jects may have reduced the variability observed within infants be-
 tween epochs, but regrettably was not feasible in a large enough sample of infants. However, it would appear prudent to allow in-
fants to settle for at least a minute after face mask placement be-
fore recording several epochs of breathing, from which \( T_{PTEF:TE} \) and other tidal breathing parameters can be calculated.

Within-subject Repeatability
Increased variability in \( T_{PTEF:TE} \) in infants younger than 6 wk of age was observed, with repeat measures differing within individuals by as much as 0.251, despite good agreement between group means on each occasion. This is in marked contrast to studies in the older infants in whom the maximal observed difference be-
tween two results was 0.085.

Stick and coworkers (7) reported limits of agreement for repeat measures of \( T_{PTEF:TE} \) after a 2 to 4 h interval of \(-0.049 \) to 0.083 in newborn infants, when using inductance plethysmography. These limits are considerably narrower than found in the young-
est infants in the current study which may reflect a higher degree of selectivity and analysis of a smaller breath number by the Australian group. Whether or not the sensitivity and specificity of \( T_{PTEF:TE} \) as an index of airway function can be improved by only selecting periods of regular breathing with clearly defined peak flows (i.e., exclusion of breaths with the most marked expi-
atory braking) has yet to be determined. However, the intrinsic variability of breathing patterns among newborn infants is clearly evident when analyzing large number of breaths and must be borne in mind when attempting to interpret the results.

There were no significant differences between preterm and full-
term infants during the first week of life with respect to either abso-
late values of \( T_{PTEF:TE} \) or its variability within or between sub-
jects. However, since all measurements between 2 and 5 wk post-
natal age were on unsedated preterm infants we cannot comment on the precise time course of changes in \( T_{PTEF:TE} \) in full-term in-
fants during this period. Some simple method of assessing air-
way function in large numbers of newborn infants before discharge from the maternity wards would provide an invaluable epidemi-
ologic tool when studying the determinants of early respiratory mor-
bidity. However, the importance of establishing a stable FRC as well as the interdependence between respiratory timing, modu-
lation of expiratory flow, and dynamic elevation of end-expiratory lung volume are likely to confound any relationship between \( T_{PTEF:TE} \) and airway function during the first few days of life.

The potential usefulness of tidal breathing parameters as an index of airway function during the neonatal period may be limited not only by the high biologic variability at this age but also by difficulties in collecting satisfactory data during quiet sleep. Sleep state is an important determinant of \( T_{PTEF:TE} \) especially in neo-
nates, in whom active retardation of expiratory flow by laryngeal activity is significantly diminished during active sleep (22). It is, therefore, desirable to confine periods of data collection to quiet sleep if comparisons are to be made within and between infants. However, during the first few days of life, the lack of any estab-
lished routine and the brief duration of clearly defined periods of quiet sleep by behavioral criteria are such that technically satis-
factory recordings of tidal breathing during quiet sleep may be
virtually as time-consuming as more complex measurements of respiratory mechanics at this age.

In conclusion, the results from this study suggest that TPTE is obtained by allowing the infant to settle for a few minutes after positioning the face mask and then recording several epochs of breathing from which 20 to 50 breaths can be analyzed. However, whether any underlying abnormalities of airway function are better reflected by the lowest TPTE recorded rather than the "average" value has yet to be assessed.

Although TPTE can be measured with an acceptable level of repeatability in infants from 6 wk of age, within-subject variability is considerably higher among newborn infants. Further work is required to clarify whether TPTE in the neonatal period, estimated either from breaths showing well-defined peak flows or from a larger number of unselected breaths, is of any value in reflecting airway function and respiratory morbidity in later infancy.

Acknowledgment: The writers gratefully acknowledge the cooperation of the parents of infants who participated in this study, the assistance of I. Dundas, M. E. Fletcher, and L. Pilgrim in data collection and analysis, and the secretarial support provided by J. Turner.

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The Relationship Between $t_{\text{PTEF}:t_E}$ and Specific Airway Conductance in Infancy

C.A. Dezateux, MRCP, 1 J. Stocks, PhD, 2 I. Dundas, BSc, 2 E.A. Jackson, MRCP, 2 and M.E. Fletcher, PhD 3

Summary. This study examines the association between the time taken to achieve peak tidal expiratory flow as a proportion of total expiratory time ($t_{\text{PTEF}:t_E}$) and specific airways conductance ($SG_{aw}$) in healthy infants and those with prior physician diagnosed, associated, lower respiratory illness with wheezing (prior LRI) during the first year of life. We compared $t_{\text{PTEF}:t_E}$ and $SG_{aw}$, the latter estimated during both initial inspiration (II) and end-expiration (EE), in 168 infants (94 males), measured on 220 occasions. Mean (range) $t_{\text{PTEF}:t_E}$ was 0.321 (0.150-0.522) in 73 healthy infants aged less than 3 months (mean, 7.8 weeks), in whom mean (range) EE $SG_{aw}$ and plethysmographic thoracic gas volume at functional residual capacity (FRC$_{\text{pleth}}$) were 2.47 s$^{-1}$ kPa$^{-1}$ (0.6-5.8) and 141 mL (87-204), respectively. Both $t_{\text{PTEF}:t_E}$ and EE $SG_{aw}$ were significantly lower in older infants with prior LRI ($n = 79$; mean age, 50.0 weeks) compared to a similarly aged group of healthy infants ($n = 68$; mean age, 48.5 weeks), the mean difference [95% confidence intervals (CI)] being $-0.039$ ($-0.013$, $-0.064$) and $-0.48$ s$^{-1}$ kPa$^{-1}$ ($-0.24$, $-0.72$), respectively. A significant but weak association between $t_{\text{PTEF}:t_E}$ and EE $SG_{aw}$ was found among infants above 3 months of age, irrespective of prior wheezing status. However, this relationship was not significant in healthy younger infants, in whom a significant but weak association with FRC$_{\text{pleth}}$ was found. Further work is needed to elucidate the factors influencing tidal expiratory flow patterns in infancy. Pediatr Pulmonol. 1994; 18:299-307. © 1994 Wiley-Liss, Inc.

Key words: Lower respiratory illness, wheezing, healthy infants; lung volume, tidal expiratory flow pattern, specific airway conductance.

INTRODUCTION

Tidal breathing measurements are being increasingly applied to population-based studies of the determinants of early respiratory morbidity. 1, 2 The time taken to achieve peak tidal expiratory flow as a proportion of total expiratory time ($t_{\text{PTEF}:t_E}$), when measured in healthy infants in the first 3 months of life, has been shown to be predictive of subsequent wheezing in boys during the first 3 years. 1, 2 In addition, $t_{\text{PTEF}:t_E}$ has been reported to be significantly related to indices of airway size in adults and children. 3, 4 However, the extent to which this parameter of tidal breathing is associated with established measures of airway function in infants remains unclear.

The aim of this study was to examine the association between $t_{\text{PTEF}:t_E}$ and specific airway conductance ($SG_{aw}$), when measured on the same test occasion, in both healthy infants and those with prior physician diagnosed lower respiratory illness with wheezing (prior LRI), i.e., wheezing, bronchiolitis, or asthma, during the first year of life.

MATERIALS AND METHODS

Study Population

Healthy Caucasian infants were recruited shortly after birth from the community as part of an ongoing epidemiological study (unpublished data). Infants born before 36 weeks gestation, requiring ventilatory assistance at birth or suffering from major congenital abnormalities were ineligible. Infants with prior physician-diagnosed LRI with wheezing were recruited from the wards and outpatient clinics of the Hospitals for Sick Children, London. All infants with prior LRI, except those with major congenital abnormalities, were eligible for study.

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Study Design

Plenysmographic measurements of lung volume and airway resistance and measurements of tidal breathing parameters were undertaken on two occasions in infants recruited to the epidemiological study: between 5 and 13 weeks postnatal age prior to any lower respiratory illness, and again, at approximately 1 year of age. Additional measurements were made between 3 and 18 months of age in some infants who participated as healthy subjects in other ongoing studies. If necessary, measurements were postponed to allow an interval of at least 3 weeks from the onset of upper respiratory tract illness. Physicians' diagnosis of LRI with wheezing (wheezing, bronchiolitis, or asthma) in the interval between the first and subsequent measurements was ascertained by retrospective review of the infant's primary medical care record, which was undertaken as soon as possible after the last visit to the laboratory. Similar measurements were performed, on one occasion, in infants with prior LRI when between 3 and 18 months of age.

Written informed consent to participate in these studies was obtained from the infants' parents, who were commonly present when measurements were performed. All study protocols had received prior approval by the Ethics Committee of the Hospitals for Sick Children.

For the purposes of this study, infants were allocated into one of three groups according to their age and status at the time of lung function testing. Group 1 consisted of healthy infants aged ≤13 weeks at testing, Group 2 of healthy infants aged >13 weeks at testing, and Group 3 of infants aged >13 weeks at testing with prior LRI. Although some infants were studied on more than one occasion, the purpose of this study was to examine cross-sectional associations between \( t_{R_{PEF:TE}} \) and \( S_{G_{aw}} \). Thus, while some infants included in Group 1 were also measured when above 3 months of age, and were included in Groups 2 or 3, depending on their status when older, longitudinal analysis was not undertaken for these infants. Groups 2 and 3 were mutually exclusive.

Lung function measurements were made on 241 occasions in 172 infants, during which data for tidal breathing and thoracic gas volume at functional residual capacity (FRC\(_{\text{plenum}}\)) were successfully obtained on all occasions and for airways resistance (\( R_{aw} \)) on 220 occasions. Failure to measure \( R_{aw} \) occurred because the infant awoke before this could be attempted (10 occasions in 10 infants), or before satisfactory data were collected (11 occasions in 11 infants). This mainly occurred in the youngest infants (17 occasions). However, a subsequent successful measurement was obtained in all but 4 of these infants, who failed to attend a further laboratory appointment. Thus, complete data for comparison of \( t_{R_{PEF:TE}} \) and \( S_{G_{aw}} \) were available for 168 infants (94 males) on 220 occasions. Measurements were obtained in 73 healthy infants aged ≤13 weeks (Group 1), in 68 healthy infants aged >13 weeks (Group 2), and in 79 infants with prior physician diagnosed LRI with wheezing aged >13 weeks (Group 3). Of the 73 infants included in Group 1, 39 (53%) and 13 (18%), who were measured again when aged more than 13 weeks, were included in Groups 2 and 3, respectively. Groups 2 and 3 were, however, independent.

Lung Function Measurements

Air flow (\( V \)) was measured using a pneumotachograph [Fleisch (Lausanne, Switzerland): size 0 or 1, according to age and size of the infant] attached to a differential pressure transducer [Validyne MP 45: \( ±0.2 \) kPa (Northridge, CA)]. Air flow was digitized, sampled at 100 Hz (Analog Devices RTI-815) and digitally integrated to yield volume. The start and end of expiration were defined as the last zero crossing of flow during inspiration and expiration, respectively. Zero flow crossings were estimated using sample-to-sample linear interpolation. This strategy ensures that any expiratory pause is incorporated into expiratory time. An adjustable scan period (usually set to 0.3 sec) prevented identification of false troughs and peaks. Peak expiratory flow was taken as the first sample at which maximum flow was recorded. Air flow measurements were calibrated prior to testing using known flows from calibrated rotamaters (Series 1100, Fisher Controls Ltd). Plethysmographic pressure (\( P_{\text{plenum}} \)) and pressure at the airway opening (\( P_{aw} \)) were measured, the latter via a port in the face mask mount, with Validyne MP 45 pressure transducers (ranges: \( ±0.2 \) and \( ±5 \) kPa, respectively). Calibrations of \( P_{\text{plenum}} \) and \( P_{aw} \) measurements were also performed prior to testing. Data display, recording, and analysis were performed using RASP software (Respiratory Analysis Program, Physio Logic Ltd, Berks, England), which has been previously validated in our laboratory, on an IBM compatible PC. Deadspace of the apparatus, excluding face mask, was approximately 2 mL kg\(^{-1}\) for all infants. Apparatus resistance, at a flow of 100 mL s\(^{-1}\), was 0.78 kPa L\(^{-1}\) s in the youngest and 0.48 kPa L\(^{-1}\) s in older infants.

Measurements were made with the infant placed supine in the plethysmograph, following sedation with triclofos sodium (75–100 mg kg\(^{-1}\): equivalent to 45–60 mg kg\(^{-1}\) chloral hydrate) given by mouth. Data were collected, with room temperature controlled at 22–25°C by a servo controlled air conditioning unit, during behaviorally determined quiet sleep, i.e., when stable posture, regular respiration, and no eye movements were observed. With the neck slightly extended and the head supported in the midline with small sandbags, a transpar-
ent facemask (Rendell-Baker, Soucek: size 1 or 2 depending on size of the infant), to which a thin rim of therapeutic silicone putty (Carters, Wiltshire) had been applied, was positioned over the infant’s nose and mouth to obtain an airtight seal. Additional support to the cheeks was provided by latex strapping attached to the face mask.

Measurements of thoracic gas volume at functional residual capacity (FRC_{pleth}) and airway resistance (R_{aw}) were made using a 100-L variable pressure infant plethysmograph by established techniques as previously described. Once an airtight seal around the face mask had been confirmed, the plethysmograph was closed. Measurements of thoracic gas volume at functional residual capacity (FRC_{pleth}) and airway resistance (R_{aw}) were made using a 100-L variable pressure infant plethysmograph by established techniques as previously described. Once an airtight seal around the face mask had been confirmed, the plethysmograph was closed and the infant allowed to breathe room air while thermal equilibrium was attained. During this time, data for the analysis of tidal breathing parameters were collected in discrete 30–60 sec epochs.

Once thermal equilibrium was achieved, at least 5 measurements of R_{aw} were obtained using end-inspiratory occlusions held for 2 to 3 respiratory efforts. Changes in P_{aw} and P_{pleth} during occlusion were displayed on a cathode ray oscilloscope to confirm that these were in phase during occlusions. Measurements of R_{aw} were made while the infant rebreathed warmed, humidified, and oxygen-enriched air from a highly compliant 2-L bag. Temperature in the rebreathing bag was adjusted to obtain a satisfactory phase relationship between V and P_{pjeth}, as determined from the pressure-flow loop displayed on the oscilloscope. Once this was achieved, data for the analysis of R_{aw} were collected in discrete epochs of 18–36 sec duration, the rebreathing bag being flushed with humidified oxygen between each epoch.

**Calculation of Lung Function Parameters**

Lung function parameters were calculated using a computer assisted system with interactive operator control (RASP) according to previously established criteria. For each infant, FRC_{pleth} was calculated as the mean of between 3 and 5 occlusions, where the infant’s airway was occluded within the first 10% of expiration, the value from each occlusion being corrected by subtracting apparatus deadspace and the volume included above end-expiration (EE). Data were excluded from analysis if there was evidence of glottic closure or an air leak around the face mask.

R_{aw} was calculated as the mean of up to 25 breaths (minimum 5). Breaths were accepted for analysis if the pressure-flow loop was closed at points of zero flow. R_{aw} was reported from measurements made at 50% of peak V at both initial inspiration (II) and EE. For each infant, the reciprocal of these values was computed to obtain G_{aw} and, after further division by FRC_{pleth}, SG_{aw}. Tidal breathing parameters were calculated from a minimum of 20 breaths (range 20–50) collected in 2 discrete epochs, t_{pEF-IE}, respiratory rate and t_{IE} being reported as the mean and standard deviation (SD). Periods of sighs or coughs were excluded from analysis.

**Statistical Methods**

For each infant, data were entered and validated with a double entry system using a database package (Epi-info, version 5.01b, Atlanta) on an IBM compatible PC. Details entered included lung function parameters, as described above, sex, ethnic group, gestational age, birthweight and age, weight, crown–heel length, and symptom status at testing. Information on maternal smoking in pregnancy and the presence of asthma in first degree relatives was obtained questionnaire and also included. Unpaired t tests and a two sample test for proportions were used to compare baseline characteristics and lung function parameters between sexes within each group and between Groups 2 and 3. Analyses were performed separately for the infants included in Group 1, as measurements performed beyond 13 weeks of age in some of these infants were included in Groups 2 and 3. Data for Groups 2 and 3 were independent and initially analyzed together, the effect of status being examined subsequently. Linear interactive modelling was used to examine the extent to which variation in t_{pEF-IE} was explained by FRC_{pleth} and II and EE SG_{aw}, both before and after adjusting for sex and age, weight, and length at testing (GLIM, Royal Statistical Society, London, 1985).

**RESULTS**

Details of the infants included in each group are given in Table 1. The prevalence of a family history of asthma and maternal smoking in pregnancy was 25 and 44%, respectively, for Group 1 infants. One infant in Group 1 was symptomatic at the time of testing, slightly crusted nostrils being the only abnormal finding on examination.

There were no significant differences between Groups 2 and 3 with respect to sex distribution and age, body weight, or length at testing. Significantly fewer infants in Group 3 were of Caucasian origin relative to Group 2, reflecting the differing criteria for inclusion for wheezy infants. Mean birthweight and gestational age were significantly lower in Group 3 infants compared to Group 2 infants. Mean birthweight and gestational age were significantly lower in Group 3 infants compared to Group 2 (mean difference, 95% CI: −321 g; −99, −544; and −1.8 weeks; −0.9, −2.6, respectively). Mothers reported smoking in pregnancy in a significantly higher proportion for Group 3 than Group 2 infants (mean difference, 95% CI: 20%; 4, 36). Similarly, a family history of asthma was significantly more prevalent among infants in Group 3 (mean difference, 95% CI: 25%; 11, 40). Three
TABLE 1—Infant Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy</th>
<th>Prior LRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;13 weeks</td>
<td>&gt;13 weeks</td>
</tr>
<tr>
<td>(n = 73)</td>
<td>(n = 68)</td>
<td>(n = 79)</td>
</tr>
<tr>
<td>Male:female</td>
<td>41:32</td>
<td>34:34</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Age (weeks)</td>
<td>7.8 (1.3)</td>
<td>50.0 (10.9)</td>
</tr>
<tr>
<td>Range</td>
<td>5.0–12.6</td>
<td>22.9–72.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>5.0 (0.8)</td>
<td>9.5 (1.4)</td>
</tr>
<tr>
<td>Range</td>
<td>3.6–8.2</td>
<td>6.1–13.8</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>57.8 (2.6)</td>
<td>75.7 (4.3)</td>
</tr>
<tr>
<td>Range</td>
<td>52.1–65.1</td>
<td>65.3–83.9</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3440 (302)</td>
<td>3437 (495)</td>
</tr>
<tr>
<td>Range</td>
<td>2480–4680</td>
<td>2325–4600</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>40.1 (1.4)</td>
<td>40.1 (1.4)</td>
</tr>
<tr>
<td>Range</td>
<td>37–43</td>
<td>36–43</td>
</tr>
<tr>
<td>Antenatal smoking (%)</td>
<td>44</td>
<td>32</td>
</tr>
<tr>
<td>FH asthma (%)</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Symptomatic at testing (n)</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

LRI, lower respiratory illness with wheezing; FH, family history. *P < 0.05; **P < 0.01; ***P < 0.001.

TABLE 2—Lung Function Parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy</th>
<th>Prior LRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;13 weeks</td>
<td>&gt;13 weeks</td>
</tr>
<tr>
<td>(n = 73)</td>
<td>(n = 68)</td>
<td>(n = 79)</td>
</tr>
<tr>
<td>FRCpl (mL)</td>
<td>141.1 (24.8)</td>
<td>262.4 (50.9)</td>
</tr>
<tr>
<td>II SGaw (s⁻¹ kPa⁻¹)</td>
<td>2.69 (1.05)</td>
<td>2.22 (0.69)</td>
</tr>
<tr>
<td>EE SGaw (s⁻¹ kPa⁻¹)</td>
<td>2.47 (1.05)</td>
<td>2.04 (0.70)</td>
</tr>
<tr>
<td>tREF-Ep (sec)</td>
<td>0.321 (0.075)</td>
<td>0.295 (0.077)</td>
</tr>
<tr>
<td>Respiratory rate (breaths min⁻¹)</td>
<td>46.5 (9.9)</td>
<td>30.5 (3.9)</td>
</tr>
<tr>
<td>tT (sec)</td>
<td>0.76 (0.18)</td>
<td>1.17 (0.18)</td>
</tr>
</tbody>
</table>

LRI, lower respiratory illness with wheezing; FRCpl, thoracic gas volume at functional residual capacity; II SGaw, specific airway conductance at initial inspiration; EE SGaw, specific airway conductance at end-expiration; tREF-Ep, time to peak tidal expiratory flow; tT, total expiratory time; CI, confidence intervals. *P < 0.001; **P < 0.0001.

Infants (5%) in Group 2 were symptomatic at testing, all of whom had minor signs of upper respiratory illness only. Of the 12 infants (15%) in Group 3 reported as symptomatic at testing, 5 had minor signs of an upper respiratory tract infection, while audible wheezing or expiratory rhonchi were present in 7 infants.
Mean (range) FRC _pleth_ for Groups 2 and 3 was 262.4 mL (158.8–375.6) and 261.9 (109.9–435.4), respectively. The mean group difference (Group 3–2) of –0.6 mL was not significant (Table 2). This represented a mean (SD; range) of 27.8 mL kPa⁻¹ (4.1; 19.7–40.7) in Group 2 and 28.0 mL kPa⁻¹ (7.1; 18.5–63.1) in Group 3. Mean II SG aw, EE SG aw, and t pTEF⁻¹E were significantly lower among Group 3 infants compared to Group 2 (Table 2). Mean (range) II SG aw for Groups 2 and 3 was 2.2 s⁻¹ kPa⁻¹ (0.8–4.4) and 1.85 s⁻¹ kPa⁻¹ (0.7–5.0), respectively, and mean (range) EE SG aw was 2.0 s⁻¹ kPa⁻¹ (0.5–4.3) and 1.6 s⁻¹ kPa⁻¹ (0.3–4.2), respectively, and this Group mean difference (Group 3–2) of 0.295 (0.138–0.500) and 0.257 (0.119–0.469) respectively. There were no significant differences in respiratory rate and tE between Groups 2 and 3 (Table 2).

The data were then examined within each group to determine whether there were any significant sex differences for gestational age, birthweight, age, weight, and length at test as well as for lung function parameters (FRC _pleth_, FRC _pleth_ kG⁻¹, t pTEF⁻¹E and II, and EE SG aw). Boys and girls in Group 1 were of comparable gestational age and age at testing. Girls in Group 1 tended to be significantly lighter at birth [group mean difference (95% CI): 270 g (42,500); P = 0.02], lighter at testing [group mean difference (95% CI): 0.6 kg (0.3, 0.9); P < 0.001] and shorter at testing [group mean difference (95% CI): 1.8 cm (0.6, 3.0); P < 0.01]. However, there were no significant sex differences in this respect with FRC _pleth_, FRC _pleth_ kG⁻¹, t pTEF⁻¹E and II, and EE SG aw. There were no significant sex differences for infants in Group 2. Although of similar age and length at testing to boys, there was a tendency for girls in Group 3 to be lighter than boys [mean difference for boys–girls; (95% CI): 0.54 kg; −0.2; 1.3; P = 0.18]. Thus, although absolute lung volume was lower in girls, FRC _pleth_ kG⁻¹ was not significantly different [mean difference for boys–girls; (95% CI): 35.7 mL; 8.5; 62.8; P = 0.01 and 2.2 mL kG⁻¹; (−1.1; 5.5); P = 0.18, respectively]. Data for boys and girls were, therefore, pooled within groups for the subsequent analyses.

Using linear regression and with t pTEF⁻¹E as the outcome variable, neither II nor EE SG aw were significantly associated with t pTEF⁻¹E in Group 1 infants (Table 3). However, a weak but significant association was observed between FRC _pleth_ and t pTEF⁻¹E, which could only explain a low proportion (11%) of the total variance in t pTEF⁻¹E (Fig. 1). This relationship remained significant after removing the outlier shown in Figure 1. A significant relationship was also found after prior adjustment for age, weight, and length at testing and sex of the infant (Table 3). Among the older infants (Groups 2 and 3), a significant but weak association was found between t pTEF⁻¹E and both EE SG aw and FRC _pleth_, but not II SG aw (Table 4). The relationship between t pTEF⁻¹E and EE SG aw for infants in Groups 2 and 3 is shown in Figure 2, with separate identification of data points for those Group 3 infants who were wheezy at testing. After allowing for the effects of age, length, and weight at testing, and sex, EE SG aw alone remained significant but explained only a low proportion (9%) of the total variance in t pTEF⁻¹E. There was, however, no significant effect of status on this relationship, the mean (95% CI) for the regression coefficient (intercept) for infants with prior LRI being −0.021 (−0.048, 0.006); P = 0.82.

**DISCUSSION**

Tidal expiratory flow patterns in infancy may reflect both age and underlying lung mechanics. During passive expiration, the elastic recoil pressure of the respiratory system is highest at the onset of expiration, a time when the airways are also well distended and hence resistance relatively low. Theoretically, peak tidal expiratory flow should therefore occur at onset of expiration, giving rise to a low t pTEF⁻¹E. In infants, this pattern may be evoked by inducing muscle relaxation with a brief end-inspiratory occlusion, but is otherwise unusual, indicating that some braking of tidal expiration is normal. It has been suggested that the low values of t pTEF⁻¹E observed in adults with airway obstruction reflect alterations in control of breathing, with a reduction of expiratory airflow...
braking in response to underlying respiratory mechanics, rather than being simply a direct index of lower airway size.3

In this study, measurement of t_{PTFE}^TE, FRC_{pleth}, and R_{aw} were made on the same test occasion in healthy infants and those with prior physician diagnosed LRI with wheezing. Group mean t_{PTFE}^TE in the younger healthy infants was comparable to that reported by Martinez et al. for a group of infants of similar age.4 Among the older infants, mean t_{PTFE}^TE was significantly lower in the group of infants with a prior history of physician-diagnosed LRI with wheezing, most of whom were asymptomatic at testing, when compared to a group of healthy infants of a similar age. A lower t_{PTFE}^TE has also been reported in adults with airflow obstruction5 and in infants with bronchopulmonary dysplasia,6 but was not observed in asthmatic children who were asymptomatic at testing.4 However, in our study, although group mean t_{PTFE}^TE was significantly lower in infants with prior LRI, there was considerable between-subject variation, suggesting that t_{PTFE}^TE discriminates well between groups but not between individuals. Martinez et al. have shown that infants with a t_{PTFE}^TE in the lower tercile of the distribution, when measured before 13 weeks of age, are at significantly greater risk of developing LRI with wheezing by 3 years of age.2 However, the purpose of this study was to report cross-sectional associations of this parameter with an established measure of airway

**TABLE 4—Regression Analyses for t_{PTFE}^TE in Older Healthy Infants (Group 2) and Those With Prior Lower Respiratory Illness (Group 3)**

<table>
<thead>
<tr>
<th>Regression coefficient (95% CI)</th>
<th>r^2</th>
<th>χ^2 value (1 degree of freedom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II SGaw</td>
<td>0.015</td>
<td>0.02</td>
</tr>
<tr>
<td>EE SGaw</td>
<td>0.035</td>
<td>0.11</td>
</tr>
<tr>
<td>FRC_{pleth}</td>
<td>0.0003</td>
<td>0.04</td>
</tr>
<tr>
<td>Adjusted for age, length, weight at testing and sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II SGaw</td>
<td>0.012</td>
<td>0.02</td>
</tr>
<tr>
<td>EE SGaw</td>
<td>0.031</td>
<td>0.09</td>
</tr>
<tr>
<td>FRC_{pleth}</td>
<td>0.0002</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted for age, length, weight at testing and status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II SGaw</td>
<td>0.008</td>
<td>0.01</td>
</tr>
<tr>
<td>EE SGaw</td>
<td>0.027</td>
<td>0.07</td>
</tr>
<tr>
<td>FRC_{pleth}</td>
<td>0.0002</td>
<td>0.01</td>
</tr>
</tbody>
</table>

For abbreviations see Table 2. *P < 0.01; **P < 0.001.

Status: infants with prior LRI (Group 3) compared to healthy infants (Group 2).
function—SGaw, analysis of the longitudinal data not being feasible until all follow-up studies have been completed.

In this study, group mean II and EE SGaw measurements were significantly lower in infants with prior wheezing LRI when compared to healthy infants of a similar age. However, within each group there was considerable between-infant variation. The range of values observed in healthy infants in our study is greater than previously reported. This may reflect differences in technique, as measurements made in the healthy infants studied by Stocks et al. were undertaken after more prolonged periods of rebreathing than is current practice in our laboratory.

A significant association of t\textsubscript{fPEF-EE} with inspiratory SGaw has been reported in healthy adults and those with airflow obstruction, with FEV\textsubscript{1} in healthy and asthmatic children (the latter asymptomatic at testing), and with \( V_{\text{maxFRC}} \) in healthy infants and those with bronchopulmonary dysplasia. We have shown that, in healthy infants aged 13 weeks or less, FRC\textsubscript{pleth}, but not II or EE SGaw, is significantly but weakly associated with t\textsubscript{fPEF-EE}. The lack of a significant relationship between t\textsubscript{fPEF-EE} and both II and EE SGaw in younger healthy infants suggests that, in the absence of airflow obstruction, there is relative freedom to vary tidal expiratory flow patterns. Laryngeal and postinspiratory diaphragmatic braking, which are accompanied by late onset of peak expiratory flow and hence prolongation of t\textsubscript{fPEF-EE}, help to maintain a dynamically elevated FRC and maximize gas exchange in newborn infants. The weak relationship between FRC\textsubscript{pleth} and t\textsubscript{fPEF-EE} observed among the younger healthy infants in this study suggests that this phenomenon may persist to some extent throughout the first 3 months of life. The importance of establishing a stable FRC, together with interdependence between respiratory timing, modulation of expiratory flow, and dynamic elevation of lung volume, may confound any relationship between t\textsubscript{fPEF-EE} and indices of airway function, especially in healthy infants. With increasing postnatal age, the need to modulate expiratory flow and timing to maintain a stable FRC diminishes.

In older infants, whether healthy or with prior LRI with wheezing, EE SGaw was most strongly associated with t\textsubscript{fPEF-EE}, the association with FRC\textsubscript{pleth} being no longer significant after allowing for age, length, and weight at testing and sex. However, EE SGaw explained only a low proportion of the total variance in t\textsubscript{fPEF-EE}. This relationship was not significantly different for infants with prior LRI compared to healthy infants. While Morris and Lane have found that the percentage of expiratory volume expired at peak tidal expiratory flow is significantly associated with inspiratory SGaw in healthy adults and those with airflow obstruction, the published data suggest that this relationship may have been influenced by individuals with SGaw of less than 0.10 cm H\textsubscript{2}O\textsuperscript{-1} s\textsuperscript{-1}.

**Fig. 2.** Scattergram of the time to peak tidal expiratory flow as a proportion of total expiratory time (t\textsubscript{fPEF-EE}) and end-expiratory specific airway conductance (SGaw) in infants aged more than 13 weeks. The open squares denote healthy infants (Group 2) and the closed squares, infants with prior physician diagnosed lower respiratory tract illness with wheezing (Group 3) who were not wheezing when tested. Closed triangles indicate Group 3 infants who were wheezing when tested.
(equivalent to $1.0 \text{s}^{-1} \text{kPa}^{-1}$). Those with values greater than this show both higher mean values and greater variability in $t_{PTEF:E}$. While direct comparisons are impossible, since measurements in infants include a variable component due to the resistance of the nasal passages, mean $S_{G_{aw}}$ does appear to be relatively constant from the end of the first year of life to adulthood. In our study, all but 3 of the healthy infants had values of $EE \geq 1.0 \text{s}^{-1} \text{kPa}^{-1}$, as did a large proportion of those with prior LRI, reflecting the fact that most of these infants were asymptomatic at testing. In the absence of current airflow obstruction, there should be relative freedom to vary tidal expiratory flow patterns and hence no strong relationship between $t_{PTEF:E}$ and other measures of airway function would be expected. Had measurements been confined to only those infants with more severe degrees of airflow obstruction, as evidenced by a low $S_{G_{aw}}$, a stronger relationship might have been found, as indicated by inspection of the data in the current study from infants with $S_{G_{aw}} < 1.0 \text{s}^{-1} \text{kPa}^{-1}$ (Fig. 2). However, we felt it important to examine the association for wheezy infants across the whole spectrum of disease severity encountered in clinical practice, therefore we employed a clinical rather than laboratory-based definition for prior airways disease.

In conclusion, we have measured $t_{PTEF:E}$, $EE$, and $S_{G_{aw}}$ in both healthy infants and those with prior LRI with wheezing above 3 months of age and found that both $t_{PTEF:E}$ and $S_{G_{aw}}$ are significantly lower in the wheezy than in the healthy group. There is a significant though weak association between $t_{PTEF:E}$ and $EE$ in infants over 3 months of age, irrespective of their prior wheezing status. However, this association is not significant in healthy younger infants, in whom the pattern of expiratory flow may reflect dynamic maintenance of FRC as much as a response to airway caliber. Further work is needed to elucidate the factors influencing tidal expiratory flow patterns in infancy.

ACKNOWLEDGMENTS

We gratefully acknowledge the cooperation of the parents of infants who participated in this study; the support of pediatricians at the Hospital for Sick Children and the Queen Elizabeth Hospital for Sick Children, Hackney, who referred infants under their care; the cooperation of the general practitioners at Chrisp Street and St Stephen’s Health Centers for permission to contact families of healthy infants; Helena Wagstaff and Liane Pilgrim who assisted with recruiting healthy infants; and the secretarial support provided by Jo Turner.

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rent wheezing respiratory illnesses during the first three years of life. Am Rev Respir Dis. 1991; 143:312-316.


A Critical Assessment of Uncalibrated Respiratory Inductance Plethysmography (Respitrace®) for the Measurement of Tidal Breathing Parameters in Newborns and Infants

E. Jackson, FRCA, J. Stocks, PhD, L. Pilgrim, RGN, I. Dundas, BSc, and C. Dezateux, MRCP

Summary. We have compared results obtained with an uncalibrated respiratory inductance plethysmograph (RIP) with those of a face mask and pneumotachograph (PNT) for the computerized measurement of the time to reach peak tidal expiratory flow as a ratio of total expiratory time (tpTEP/tTE). Simultaneous measurements were made in 32 healthy neonates aged 0–3 weeks, 35 healthy infants aged 5–82 weeks, and 28 infants aged 15–94 weeks with physician diagnosed recurrent wheeze. The group mean (±SD) values of tpTEP/tTEP determined using a PNT were 0.455 (±0.129), 0.263 (±0.077), and 0.232 (±0.089) for the neonates, healthy infants and infants with recurrent wheeze respectively. RIP gave mean (±SD) values that were 0.055 (±0.044) and 0.025 (±0.104) lower than the PNT in healthy neonates and infants with recurrent wheeze respectively; RIP values were 0.002 (±0.073) higher in the healthy infants over 4 weeks of age than measurements by PNT. Although the difference between the two measurements was not related to the thoracoabdominal phase angle, as measured from Lissajous figures, examination of the RIP rib cage and abdominal signals revealed that many healthy subjects, while appearing clinically in phase, had rib cage and abdominal signals that differed markedly from each other in terms of convexity/concavity during early expiration. This may explain the lack of agreement between the two methods. We conclude that uncalibrated RIP should be used with caution for the determination of tpTEP/tTEP, even in subjects whose rib cage and abdomen appear to move synchronously. The measurement of tpTEP/tTEP did not differentiate between the healthy infants and infants with recurrent wheezing. Pediatr Pulmonol. 1995; 20:119–124.

Key words: Infant pulmonary function tests, respiratory inductance plethysmography, normal (reference) values, wheezing.

INTRODUCTION

There has been increasing interest in the development of simple methods of measuring respiratory function in infants. One such method is the analysis of tidal expiratory flow patterns, first described in adults and more recently assessed in infants. Using a pneumotachograph (PNT) with face mask, Martinez et al. measured the time to reach peak tidal expiratory flow as a ratio of total expiratory time (tpTEP/tTEP) and showed that low values in early infancy were associated with an increased risk of the subsequent development of wheezing illness. In 1992, Stick et al. suggested that such measurements could be simplified by using uncalibrated respiratory inductance plethysmography (RIP, Respitrace®), which potentially overcomes the need to use a face mask and may avoid the need for sedation in many infants. Their work was based on a study of newborns. However, tidal breathing measurements for epidemiological studies may be more helpful in late than early infancy when the values are more reproducible. Although Stick et al. used computerized data collection, their analysis required the user to identify peak expiratory flow and the start and end of expiration, using cursors. Computerization of data analysis would make the method more applicable to large population based studies and may reduce observer bias. The aim of this study was to assess the accuracy of

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TABLE 1—Subject Details

<table>
<thead>
<tr>
<th></th>
<th>M:F (n)</th>
<th>Preterm (n)</th>
<th>Age (weeks) median (range)</th>
<th>Weight (kg) median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy neonates</td>
<td>17:15</td>
<td>7</td>
<td>0.4 (0-3)</td>
<td>3.2 (1.6-4.7)</td>
</tr>
<tr>
<td>Healthy infants</td>
<td>20:15</td>
<td>10</td>
<td>17 (5-82)</td>
<td>6.5 (2.8-12.7)</td>
</tr>
<tr>
<td>Infants with recurrent wheeze</td>
<td>19:9</td>
<td>7</td>
<td>47 (15-94)</td>
<td>9.6 (4.7-12.3)</td>
</tr>
</tbody>
</table>

1Less than 37 weeks gestation.

uncalibrated respiratory inductance plethysmography for the computerized measurement of $t_{PEF}^{te}$ in both newborns and infants.

SUBJECTS AND METHODS

Subjects

Thirty-two healthy neonates, 35 healthy infants over 4 weeks of age, and 28 infants with physician diagnosed recurrent wheeze were studied. Subject details are summarized in Table 1. Subjects were classified as preterm if they were born before 37 weeks gestation. All healthy neonates and infants were free of cardiorespiratory abnormalities, had no history of wheeze or lower respiratory tract infection, and had not required respiratory support other than face mask oxygen in the delivery room. Only 7 of the 28 infants with recurrent wheeze were symptomatic at the time of study. The healthy term neonates were recruited for the evaluation of RIP alone and the remaining subjects were participating in ongoing epidemiological and methodological research studies. Where a subject had serial measurements as part of a longitudinal study, only the first set of measurements was included. The study was approved by the Hospitals Ethics Committees, and informed consent was obtained from the parents of each subject.

Protocol

In order to assess the agreement between the two techniques for the measurement of $t_{PEF}^{te}$, subjects were studied simultaneously using RIP and a pneumotachograph (PNT) with face mask. A minimum of three 21–27 sec epochs of data were recorded for each subject (epoch length being determined by sampling frequency). All measurements were made during behaviorally determined quiet sleep, with the infants loosely clothed and either supine or semirecumbent. The neonates were studied unsedated, but the majority of the healthy and all the infants with recurrent wheeze were sedated with triclofos sodium 50–100 mg·kg⁻¹.

Measurement Methods

The impedance changes of two inductance coils placed around the ribcage and mid abdomen were measured with a Respiritrace® (model 10.9230, Ambulatory Monitoring Incorporation, New York). The Respiritrace® incorporates a 15 Hz low pass analog filter. The gains were set to maximum and the output to AC. Flow was measured using a Rendell Baker Soucek face mask (size 0 or I), a PNT with Validyne (±0.2 kPa) MP45 pressure transducer, and a Validyne amplifier (with the low pass filter set to 10 Hz). Hans Rudolph (0–10 L min⁻¹) and Fleisch size #0 and #1 PNTs, with resistances of 1.1, 0.4, and 0.1 kPa L⁻¹ sec at 100 mL sec⁻¹, respectively, were used, depending on the size of the subject. The dead space did not exceed 2 mL·kg⁻¹ in any subject. All PNTs were calibrated using known flows from calibrated rotameters (Series 1100 Fisher Controls Limited) and used within their linear ranges. The analog signals were digitized with a RTI 815 analog-to-digital converter. Sampling frequencies of 100 to 80 Hz were used for neonates and infants respectively. Data were recorded and analyzed using an IBM compatible personal computer and RASP (Respiratory Analysis Program) software (Physio Logic, Newbury, England).

The data analysis software adds the ribcage (RC) and abdomen (AB) signals to give a sum “volume” signal, which is differentiated and smoothed to give RIP “flow” from which $t_{PEF}^{te}$ is determined. Other tidal breathing parameters and measures of the phase relationship of the RC and AB signals are also calculated. The phase relationship is expressed in degrees and calculated from Lissajous figures as described by Sivan et al.6 A positive phase angle implies that abdominal excursion leads ribcage excursion. The program analyses the simultaneous PNT signal to give tidal volume and parameters of respiratory timing, including $t_{PEF}^{te}$. The operator selects runs of breaths to be analyzed using cursors, and the sample points used for analysis are displayed for inspection. For each subject, a total of 30 breaths from at least two epochs of data were analyzed. Runs of at least 8 consecutive breaths were used. Sighs and the first 10 breaths after a sigh were excluded.

Statistical Analysis

Mean values of $t_{PEF}^{te}$ for groups of subjects were compared using unpaired $t$ tests. Agreement between the two methods of measuring tidal breathing parameters was assessed using the methods of Bland and Altman.7

Software Validation

The analysis software was assessed in two ways: (1) sample point recognition, the addition of the RIP ribcage
and abdomen signals, and the calculation of parameters from the PNT flow and RIP "volume" and "flow" signals were checked and found to be correct using an ASCII print-out of data; (2) to assess the effect of the digital smoothing during differentiation of the RIP signal on the measurement of \( t_{\text{PTEF} - t_{E}} \) tidal breathing data were recorded with the analog signal of the flow transducer integrated with a Validyne FV156 integrator and collected as if it were the RIP abdomen signal of the Respitrace®. The PNT flow signal and the substituted RIP abdomen signal were both sampled at 80 Hz. An analysis of 30 breaths was performed with the program set to construct the RIP sum "volume" signal with no contribution from the RIP ribcage signal. The mean (±SD) \( t_{\text{PTEF} - t_{E}} \) measured from the PNT flow signal was 0.116 (±0.008) and from the simultaneous substituted RIP signal 0.125 (0.012). The difference was statistically significant \( (P = 0.003) \).

RESULTS

When using the PNT, satisfactory data were obtained in all subjects. Nine subjects (1 of 32 healthy neonates, 4 of 35 healthy infants, and 4 of 28 infants with recurrent wheeze) were excluded from the comparison of the two methods because the RIP "flow" signal appeared noisy with multiple peaks during expiration. In five of these infants this may have been due to the summing of RC and AB signals that were out of phase or of very different shapes. An example of satisfactory data is shown in Figure 1.

The group mean (±SD) values of \( t_{\text{PTEF} - t_{E}} \) determined by using a PNT were 0.455 (±0.129), 0.263 (±0.077), and 0.232 (±0.089) for the healthy neonates, healthy infants, and infants with recurrent wheeze, respectively. There was no significant difference in \( t_{\text{PTEF} - t_{E}} \) between the infants with recurrent wheeze and healthy infants \( (P = 0.18) \). Infants with symptoms at the time of testing had a mean \( t_{\text{PTEF} - t_{E}} \) of 0.244, which was not significantly different from that seen in asymptomatic infants with recurrent wheeze \( (t_{\text{PTEF} - t_{E}} 0.228, P = 0.76) \). RIP gave mean (±SD) values that were 0.055 (±0.044) and 0.025 (±0.014) lower than the PNT in the healthy neonates and infants with recurrent wheeze respectively, and 0.002 (±0.073) higher than the PNT in the healthy infants over 4 weeks of age. The difference between \( t_{\text{PTEF} - t_{E}} \) determined using a PNT and RIP for each subject is plotted as described by Bland and Altman\(^7\) in Figure 2, with 95% limits of agreement for the three groups of subjects given in Table 2. Large individual differences in many subjects resulted in wide limits of agreement, especially in infants beyond the neonatal period. The mean (±SD) difference between the expiratory time \( (t_{x}) \) determined using a pneumotachograph and RIP were +0.009 (±0.011), −0.008 (±0.031), and +0.005 (±0.035) sec for neonates, healthy infants, and infants with recurrent wheeze, respectively (Table 3).

Martinez et al.\(^5\) suggested that healthy infants whose \( t_{\text{PTEF} - t_{E}} \) values are in the lowest tercile have an increased risk of developing wheezing illness. We, therefore, assessed the degree to which healthy neonates and infants might be misclassified into the lowest tercile by using RIP instead of a PNT to determine \( t_{\text{PTEF} - t_{E}} \). The group of 31 neonates and the group of 31 healthy infants were each ranked according to the value of \( t_{\text{PTEF} - t_{E}} \) determined using a PNT and using RIP. The 10 neonates with the lowest values of \( t_{\text{PTEF} - t_{E}} \) determined with the PNT were...
the same 10 neonates as those with the lowest values of \( t_{\text{PTEF}:E} \) determined by RIP. Only 6 of the 10 healthy infants with the lowest values of \( t_{\text{PTEF}:E} \) determined by PNT were amongst the 10 infants with the lowest values determined by RIP.

The influence of the phase relationship of the ribcage and abdominal signals was assessed by plotting the difference in \( t_{\text{PTEF}:E} \) measured using the two methods against the phase angle (Fig. 3). The phase angle ranged from \(-1\) to \(54^\circ\) for healthy neonates, \(-40\) to \(57^\circ\) for healthy infants, and \(-28\) to \(107^\circ\) for infants with recurrent wheeze. There was no clear relationship between this measure of asynchrony and the difference in \( t_{\text{PTEF}:E} \) determined with the two methods.

**DISCUSSION**

We have compared uncalibrated respiratory inductance plethysmography with a face mask and PNT for the simultaneous computerized measurements of \( t_{\text{PTEF}:E} \) in healthy neonates and infants, as well as in a group of

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**TABLE 2—Within Subject Agreement Between Simultaneous Measurements of \( t_{\text{PTEF}:E} \) Determined Using a Pneumotachograph (PNT) and Respiratory Inductance Plethysmograph (RIP)**

<table>
<thead>
<tr>
<th>Subject group</th>
<th>( t_{\text{PTEF}:E} ) PNT mean (range)</th>
<th>( t_{\text{PTEF}:E} ) RIP mean (range)</th>
<th>Difference (PNT - RIP) mean (95% CI)</th>
<th>Agreement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates ((n = 31))</td>
<td>0.455 (0.201,0.748)</td>
<td>0.400 (0.203,0.713)</td>
<td>0.055 (0.039,0.070)</td>
<td>-0.032,0.142</td>
</tr>
<tr>
<td>Healthy infants ((n = 31))</td>
<td>0.263 (0.135,0.435)</td>
<td>0.265 (0.103,0.577)</td>
<td>-0.002 (-0.028,0.024)</td>
<td>-0.147,0.144</td>
</tr>
<tr>
<td>Infants with recurrent wheeze ((n = 24))</td>
<td>0.232 (0.123,0.459)</td>
<td>0.207 (0.085,0.423)</td>
<td>0.025 (-0.018,0.067)</td>
<td>-0.182,0.232</td>
</tr>
</tbody>
</table>

*Confidence intervals.

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**TABLE 3—Within Subject Agreement Between Simultaneous Measurements of Expiratory Time (\( t_{E} \)) Determined Using a Pneumotachograph (PNT) and Respiratory Inductance Plethysmograph (RIP)**

<table>
<thead>
<tr>
<th>Subject group</th>
<th>( t_{E} ) PNT mean (range)</th>
<th>( t_{E} ) RIP mean (range)</th>
<th>Difference (PNT - RIP) mean (95% CI)</th>
<th>Agreement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates ((n = 31))</td>
<td>0.57 (0.34,1.01)</td>
<td>0.56 (0.33,1.00)</td>
<td>0.01 (0.00,0.01)</td>
<td>-0.01,0.03</td>
</tr>
<tr>
<td>Healthy infants ((n = 31))</td>
<td>1.01 (0.49,1.83)</td>
<td>1.02 (0.46,1.94)</td>
<td>-0.01 (-0.02,0.00)</td>
<td>-0.07,0.05</td>
</tr>
<tr>
<td>Infants with recurrent wheeze ((n = 24))</td>
<td>1.09 (0.52,1.39)</td>
<td>1.08 (0.52,1.37)</td>
<td>+0.00 (-0.01,0.02)</td>
<td>-0.07,0.08</td>
</tr>
</tbody>
</table>

*Confidence intervals.

---

**Fig. 3. Difference in \( t_{\text{PTEF}:E} \) [pneumotachograph (PNT) - respiratory inductance plethysmograph (RIP)] plotted against phase angle. Symbols as for Figure 2.**
Infants with physician diagnosed recurrent wheeze. The mean (±SD) values of t_{PTEF;E} measured with a pneumotachograph were 0.455 (±0.129) and 0.263 (±0.077) for healthy neonates and infants over 4 weeks of age, respectively; these results are similar to previously reported values. 2-4 In this study t_{PTEF;E} measurements failed to separate healthy infants from those with recurrent wheeze.

There was a poorer level of agreement between t_{PTEF;E} as measured with a PNT and RIP in the current study than that reported by Stick et al. 3 in a group of 15 healthy neonates [mean difference (PNT - RIP) = -0.014; 95% limits of agreement -0.070, +0.042]. However, despite the wider limits of agreement and the large bias between the two methods in the neonates in our study (mean difference +0.055, 95% confidence intervals 0.039, 0.070), the same neonates were classified as being in the lowest tercile for t_{PTEF;E} with the two methods of measurement. The large discrepancies were primarily accounted for by errors in the measurements of time to peak expiratory flow, as there was good agreement between the two methods for the determination of expiratory time (Table 3).

The major differences between this study and that previously published by Stick et al. 3 are the use of different analysis software and different criteria for breath selection. Stick et al. used a differentiated RIP “flow” signal generated by the Respitrace® with the gains for the ribcage and abdominal signals set at maximum. The Respitrace® model available to us did not provide a differentiated signal, therefore the ribcage and abdomen signals were both recorded and then added and differentiated by RASP software. Assessment of the software showed a slight over-estimate of t_{PTEF;E} by RIP (0.008), but the discrepancy, although statistically significant, was small and did not explain the differences between t_{PTEF;E} determined with the two methods. The use of a computer program to identify peak expiratory flow should be advantageous in large epidemiological studies as it reduces observer bias. However, the exclusion of breaths without a clearly defined peak expiratory flow may have contributed to the better agreement between the two methods found by Stick et al. The other difference between this study and previous work is that we have included infants over a wider age range. Measurements after the neonatal period may be of greater relevance to epidemiological studies as t_{PTEF;E} is more reproducible in older infants, 4 and values of t_{PTEF;E} in the neonatal period have not yet been shown to be predictive of future respiratory morbidity.

The assumption underlying the use of uncalibrated respiratory inductance plethysmography for the measurement of t_{PTEF;E} in epidemiological studies is that healthy subjects have synchronous ribcage and abdominal movement. Although examination of phase angle failed to identify infants in whom the agreement of the two methods was poor, examination of the RIP ribcage and abdomen signals revealed that many healthy subjects, while appearing clinically in phase showed marked variations in the shape of the ribcage and abdominal signals during early expiration (see Fig. 4). In these circumstances one would only expect agreement if the ribcage and abdominal weighting of the sum signal was correct (i.e., the Respitrace® was qualitatively calibrated). The exclusion of breaths without a well-defined RIP peak expiratory flow by Stick et al. may have resulted in the preferential selection of breaths in which the ribcage and abdominal signals are most similar in shape during early expiration.

The mean (±SD) percentage contribution of the ribcage to tidal volume changes has been reported as 34 (±9)% in young infants increasing to 60 (±17)% by 9 months of age 5 which is similar to that seen in adolescents and adults. 9,10 This large between-subject variability reduces the accuracy with which the relative contribution of the ribcage may be predicted in any individual. Therefore, weighting of the two signals so that they each give a fixed proportion of the sum signal is not more likely to yield satisfactory results. Similarly, using the output of either the ribcage or abdomen signal alone would not be valid even if it did give a less noisy RIP “flow” signal. We suggest that differences in the shape of the ribcage and abdominal signal in early expiration limit the accuracy of uncalibrated RIP for the measurement of t_{PTEF;E}. Several methods of calibration have been described involving changes in body position or sleep state 12 or periods of simultaneous measurement with a PNT or spirometer. 13,14 However, the application of these calibration methods would remove the advantages of using RIP for the measurement of tidal breathing parameters in epidemiological studies. A recently described method, qualitative diagnostic calibration (QDC) 13,15 that is performed during tidal breathing without postural or sleep state changes may improve the accuracy of RIP for the measurement of respiratory timing without making the method too complicated for use in epidemiological studies.

In conclusion, the computerized measurement of t_{PTEF;E} by uncalibrated respiratory inductance plethysmography is not possible in all infants and should be used with caution, particularly at ages beyond the neonatal period. The problems may be greatest in infants who have had respiratory problems, even if asymptomatic at the time of testing. Examination of the separate ribcage and abdominal signals of healthy infants suggests that some form of qualitative calibration may be desirable if respiratory inductance plethysmography is to be used to determine t_{PTEF;E}. Even if the measurement of t_{PTEF;E} is useful in epidemiological studies, it does not clearly separate symptomatic and asymptomatic infants with recurrent wheeze from healthy infants and would therefore not be helpful for diagnostic respiratory function testing.
Fig. 4. Examples of simultaneous respiratory inductance plethysmograph ribcage and abdomen signals to illustrate the marked differences in shape during expiration that were seen even during periods of "synchronous" breathing in healthy infants: (a) 11-month-old male, (b) 4-month-old male, (c) 2-month-old male, and (d) 2-month-old female.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of the pediatricians of Queen Elizabeth Children’s Hospital and the general practitioners at Chrisp Street Health Centre for permission to study infants under their care, the cooperation of Dr. K. Costeloe and the staff of the Maternity and Special Care Baby Units of the Homerton Hospital during recruitment and data collection, and the technical assistance of M. Fletcher and A.-F. Hoo.

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Comparison of Single-Breath and Plethysmographic Measurements of Resistance in Infancy

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Single-breath technique (SBT) measurements of total respiratory resistance (Rrs) were compared with plethysmographic measurements of airway resistance (Raw) in healthy infants < 13 wk of age (Group 1; n = 49) and > 13 wk of age (Group 2; n = 37) and in infants > 13 wk of age with prior wheeze (Group 3; n = 49). A significantly higher percentage of Rrs (19%) than of Raw (2%) measurements were technically unacceptable, alinearity of the flow-volume curve accounting for 54% of Rrs failures. Although both Rrs and Raw were significantly higher in Group 3 infants, between-subject variability was wide in all groups. Rrs was significantly higher than initial expiratory (IE) Raw in all groups. Mean difference Rrs - IE Raw (95% CI) values were 1.98 (1.51, 2.48), 1.29 (0.96, 1.62), and 1.97 (1.56, 2.38) kPa·L⁻¹·s for Groups 1, 2, and 3, respectively. Significant but smaller differences were seen for end-expiratory (EE) Raw in Groups 1 and 2 but not in Group 3. Mean difference Rrs - EE Raw (95% CI) values were 0.68 (0.11, 1.26), 0.55 (0.19, 0.92), and 0.31 (-0.06, 0.69) kPa·L⁻¹·s for Groups 1, 2, and 3, respectively. Despite wide between-subject variability in Rrs and a relatively high failure rate, the SBT is simple to use, and it may be applicable to epidemiologic studies. However, clinical applications in individual infants may be limited by failure to detect the dynamic changes in resistance throughout the breath evident from plethysmographic studies. Dundas I, Dezateux CA, Fletcher ME, Jackson EA, Stocks J. Comparison of single-breath and plethysmographic measurements of resistance in infancy. Am J Respir Crit Care Med 1995;151:1451-8.
2 comprised 37 healthy infants older than 13 wk of age, and Group 3 comprised 49 infants with physician-diagnosed wheeze older than 13 wk of age. The aim of this study was to compare measurements of Rrs and Raw obtained on the same occasion. Thus, although some infants were studied on more than one occasion, longitudinal analysis was not undertaken for these infants, who were included in Group 1 when younger than 13 wk of age and subsequently in Group 2 or in Group 3, according to their respiratory status. Groups 2 and 3 were, therefore, mutually exclusive.

Group 1 infants were 5.0 to 12.6 wk of age and weighed 3.8 to 6.7 kg at testing. Group 2 infants were 17.7 to 61.7 wk of age and weighed 6.1 to 12.7 kg at testing, and Group 3 infants were 15.1 to 74.3 wk of age and weighed 3.6 to 13.8 kg at testing.

This study was approved by the local ethics committee. Written informed consent was obtained from one or both parents, who were often present during measurements.

Procedures
Prior to measuring each infant, the 100-L variable pressure plethysmograph was calibrated in terms of volume change. Bags of saline with a total weight approximately equal to that of the infant were placed in the plethysmograph. To approximate pressure changes occurring during measurements, 20 ml of air (or 40 ml for infants older than 4 mo of age) were syringed into and out of the chamber at a frequency equivalent to the infant's respiratory rate. Pressure at the airway opening (Pao) and flow (V) were also calibrated on each occasion (21). Airflow was measured using a Fleisch pneumotachograph (PNT) appropriate to the infant's size and peak flow (size "0" linear to ± 12 L/min, size "1" linear to ± 50 L/min) connected to a low range pressure transducer (Validyne MP45 ± 0.2 kPa; Validyne Corp., Northridge, CA). Paco, via a port in the mask mount, and plethysmographic pressure (Pples) were measured using Validyne MP45 transducers with ranges of ± 5 and ± 0.2 kPa, respectively. The apparatus resistance at a flow of 100 ml/s was 0.78 kPa L^-1 s^-1 using the Fleisch "0" PNT and 0.48 kPa L^-1 s^-1 with the Fleisch "1" PNT, with an apparatus dead space of 7.6 and 25 ml, respectively.

All measurements were made during quiet sleep when posture was stable, respiration regular, and no eye movements observed (22). The infants were sedated using triclorofos sodium 75 mg/kg (up to 8 wk of age) or 100 mg/kg (older infants). One gram of triclorofos sodium was equivalent to 650 mg chloral hydrate. Once asleep, the infant was placed supine within the open plethysmograph with the neck slightly extended and head in the midline, supported on either side by small sandbags. A transparent Rendell-Baker face mask, size 1 or size 2 as appropriate, was gently lowered in place after applying therapeutic putty around the rim to obtain an airtight seal. Latex cheek strapping was attached to the face mask mount to provide additional support.

After checking the seal by performing a brief end-inspiratory occlusion (23), the plethysmograph was closed, and the infant was allowed to breathe room air while thermal equilibrium within the chamber was attained. Measurements of thoracic gas volume at functional residual capacity were made using the plethysmograph (FRCpleth) according to well-established criteria as described previously (21, 24, 25).

For FRCpleth measurements, at least five early expiratory occlusions were made after a stable end-expiratory level had been established, each being held for two to three respiratory efforts. Changes in Pples and Pao were displayed on a cathode-ray oscilloscope. Data were considered acceptable if no leaks were evident and changes in Pples versus Pao were in phase during occlusions. The infant was then allowed to rebreathe from a highly compliant 2-L bag containing warmed, humidified and oxygen-enriched air (temperature at the mask = 37°C). The phase relationship between V and Pples was inspected on an oscilloscope, and temperature within the rebreathing bag was adjusted if necessary until a satisfactory pressure-flow loop was obtained (24). Three epochs of data during rebreathing were collected, each of 18 to 36 s duration. The rebreathing bag was flushed with humidified oxygen between each epoch.

Measurements of Rrs and respiratory system compliance (Crs) by the SBT were attempted in all infants using the pneumatically operated valve system employed during plethysmographic measurements. End-inspiratory occlusions were held until a stable pressure plateau was seen. A minimum of five successful occlusions were obtained, allowing five to ten breaths between occlusions to reestablish the end-expiratory level and to detect air leaks around the face mask (23). When possible, occlusions were also performed while the infant was rebreathing warmed, humidified air to obtain SBT measurements of Rrs under the same conditions as Raw. Crs was also measured by the multiple occlusion technique (MOT) using previously published methods (13, 14) for comparison with SBT data (25, 27).

Data display, recording, and analysis were performed using RASP software (Respiratory Analysis Program, Physio Logic Ltd, Berks, UK) on an IBM compatible computer. V, Pao, and Pples were digitized and sampled (Analog Devices ATl-815) at 50 to 100 Hz (FRCpleth, MOT, and Raw) or 100 to 200 Hz (SBT) according to the infant's respiratory rate. Volume was digitally integrated from V. Data were collected in discrete 18 to 72 s epochs.

Analysis of Lung Function Parameters
All data were analyzed using a computer-assisted system (RASP) with interactive operator quality control, according to previously established criteria (13, 14, 21).

Lung Volume
FRCpleth was calculated as the mean of three to five occlusions when the infant was occluded at or within 10% of the start of expiration. Subsequent correction to FRC was performed by subtracting the volume occluded during end-expiratory volume and the apparatus dead space from the total occluded gas volume. The phase relationship between Pples and Pao was inspected on an X-Y plot, and occlusions were not analyzed if there was any evidence of glottic closure or leaks through or around the apparatus (21).

Airway Resistance
Values of Raw were reported as the mean of between five and 25 breaths (median, 11 breaths), where the pressure-flow loops were accepted if closed at points of zero flow. Raw was calculated from the beginning and end of both inspiration and expiration, i.e., at four points throughout the respiratory cycle, giving initial and end-inspiratory and initial and end-expiratory Raw (25), at a flow equivalent of ± 20 ml/s to the mean flow recorded during the calculation of Rrs by the SBT in each infant.

Respiratory Resistance and Compliance
Passive flow-volume data obtained from the SBT were accepted if the expiratory flow-volume plot was linear (r² ≥ 0.69) over at least 40% of total expired volume and the standard deviation (SD) of the pressure plateau samples was < 0.01 kPa over at least 0.1 s. Apparatus resistance at the flows attained during expiration was subtracted from Rrs. Crs from the MOT was calculated from the slope of the least-squares linear regression through the volume-pressure data. Data were accepted when the Pao plateau was of > 0.15 s duration with a SD of < 0.01 kPa and the slope of the volume-pressure regression line had an r² ≥ 0.95 over a pressure range of at least 0.35 kPa.

Statistical Methods
Unpaired t tests and a two-sample test for proportions were used to compare baseline characteristics and lung function parameters between groups. Comparisons of lung function parameters, obtained by different techniques or under different conditions were made using the method of Bland and Altman (28).

RESULTS
Technically satisfactory results for both Raw and Rrs were obtained on 107 of 135 occasions. As summarized in Table 1, a significantly higher percentage of Rrs measurements failed relative to plethysmographic measurements of Raw (weighted mean from all occasions, 19 and 24%, respectively; 95% confidence intervals [CI] of the difference Rrs - Raw: 7%, 27%). This difference was particularly marked in infants older than 3 mo of age (i.e., Groups 2 and 3). However, there was no significant difference in the percentage of failed SBT measurements between infants with physi-
cian-diagnosed wheeze (Group 3) and healthy infants of a comparable age (Group 2) (95% CI for the difference Group 3 to Group 2: −15%, 20%). A linearity of the flow-volume curve (Figure 1) and failure to equilibrate or achieve a relaxed plateau during airway occlusion (13, 14) were the major reasons for failure to obtain satisfactory estimates of Rrs (54 and 23% of all failures, respectively). Successful measurements of Raw were obtained in all but three infants, two of whom woke before measurements could be completed, and in one of whom severe weather conditions precluded reliable plethysmographic data collection.

Thus, comparison of Rrs and Raw was possible on 107 of 135 occasions (79%), and details of these infants are summarized in Table 2. Of the 42 infants in Group 1, 21 and seven were included in Groups 2 and 3, respectively, when subsequently measured at more than 13 wk of age. Groups 2 and 3 were, however, independent. Of the 36 infants with prior wheeze, 11 were born at or below 36 wk of gestation, and two required supplemental oxygen. However, only 10 were symptomatic at time of testing.

There were no significant differences between those successfully studied and those in whom one or more measurements failed with respect to sex, maternal smoking during pregnancy, family history of asthma, body size, or specific conductance (reciprocal of resistance divided by FRCpleth) (p > 0.10 for all parameters). For older infants with successful measurements of Rrs and Raw, weight and length at time of testing were similar between healthy and wheezy infants (p > 0.10). The prevalence of maternal smoking during pregnancy and family history of asthma was significantly higher in wheezy (Group 3) than in healthy (Group 2) infants (95% CI of the differences Group 3 to Group 2: 10%, 59%; 3%, 50%, respectively). Of the seven infants from Group 1 subsequently included in Group 3, six (86%) had mothers who smoked throughout pregnancy compared with only eight (38%) of the 21 infants who were subsequently included in Group 2. The prevalence of postnatal maternal smoking was within 3% of that reported during pregnancy for each of the groups (data not shown).

Results from the lung function measurements are summarized in Table 3. In Group 1, mean (SD) FRCpleth was 27.9 (5.0) ml/kg, and mean (SD) Rrs was 5.3 (1.7) kPa-L⁻¹-s⁻¹, whereas Raw ranged from 2.4 to 4.5 kPa-L⁻¹-s⁻¹ throughout the respiratory cycle. Among the older infants there was a tendency for mean (SD) FRCpleth per kilogram to be higher in wheezy than in healthy infants: 29.9 (6.6) and 26.2 (4.1) ml/kg respectively, but this was not statistically significant (95% CI of the difference Group 3 to Group 2: −1.1, 4.3 ml/kg; p > 0.10). Both Rrs and Raw, calculated at either initial inspiration or end-expiration, were significantly higher among wheezy infants than among healthy infants of a similar age. However, these differences were not significant when Raw was calculated at higher lung volumes, i.e., during end-inspiration and initial expiration.

There were small but statistically significant differences between Crs calculated by the MOT and SBT in all three groups (Table 3). Mean difference (95% CI) was 0.7 (0.2, 1.2) ml·kPa⁻¹·kg⁻¹ (p < 0.01) for Group 1, −1.0 (−1.7, −0.4) ml·kPa⁻¹·kg⁻¹ (p = 0.002) for Group 2, and 0.9 (0.3, 1.5) ml·kPa⁻¹·kg⁻¹ (p < 0.01) for Group 3. The mean intercept [(MOT + SBT)/2] was approximately 3 ml/kg for all three groups of infants. However, while it was slightly higher during MOT for Groups 1 and 3 (0.6 and 0.9 ml/kg, respectively), for Group 2 Infants it was, on average, 0.8 ml/kg higher during the SBT.

The relationship between Rrs and Raw calculated at matched flows during initial and end-expiration for Groups 2 and 3 (according to the method of Bland and Altman) is shown in Figures 2 and 3, with limits of agreement shown in Table 4. Despite the wide scatter of results, Rrs was significantly (p < 0.001) higher than initial expiratory Raw in all three groups of infants. Rrs exceeded initial expiratory Raw in all but two healthy older infants and three younger healthy infants. Although the differences were smaller, mean Rrs was also significantly (p < 0.05) higher than Raw calculated at end-expiration in Groups 1 and 2. However, there was no significant difference between the two techniques in Group 3 infants (p = 0.10). End-expiratory Raw exceeded Rrs in 28% of infants in both Groups 1 and 2, and in 22% of infants in Group 3.

During measurements of Raw the infant breathed from a bag containing warmed, humidified, oxygen-enriched air. This was accomplished by statistically significant increases in respiratory rate.

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**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>59.2</td>
<td>3.4</td>
<td>53.0 to 66.4</td>
</tr>
<tr>
<td>Group 2</td>
<td>58.3</td>
<td>3.2</td>
<td>53.0 to 66.4</td>
</tr>
<tr>
<td>Group 3</td>
<td>57.8</td>
<td>3.1</td>
<td>53.0 to 66.4</td>
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**Table 2**

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<td>53.0 to 66.4</td>
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*Note: Definitions and abbreviations are provided in the text. Further details can be found in the original article.*
TABLE 3
LUNG FUNCTION RESULTS*

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRCpleth, ml</td>
<td>142.1 (27.7)</td>
<td>265.3 (51.4)</td>
<td>278.4 (76.1)</td>
<td>-19.0, 44.9</td>
</tr>
<tr>
<td>Raw, kPa-L·s⁻¹</td>
<td>3.4 (1.1)</td>
<td>2.1 (0.9)</td>
<td>2.8 (1.5)</td>
<td>0.1, 1.4‡</td>
</tr>
<tr>
<td></td>
<td>2.4 (1.3)</td>
<td>1.5 (0.6)</td>
<td>2.0 (1.3)</td>
<td>0.0, 0.9</td>
</tr>
<tr>
<td></td>
<td>3.2 (1.4)</td>
<td>2.0 (0.8)</td>
<td>2.3 (0.9)</td>
<td>-0.1, 0.7</td>
</tr>
<tr>
<td></td>
<td>4.5 (1.7)</td>
<td>2.7 (1.0)</td>
<td>3.9 (1.7)</td>
<td>0.5, 1.9‡</td>
</tr>
<tr>
<td>Rrs, kPa-L·s⁻¹</td>
<td>5.3 (1.7)</td>
<td>3.3 (1.0)</td>
<td>4.2 (1.7)</td>
<td>0.3, 1.6§</td>
</tr>
<tr>
<td>Crs SBT, ml kPa⁻¹·kg⁻¹</td>
<td>12.7 (2.3)</td>
<td>15.4 (2.7)</td>
<td>12.1 (2.5)</td>
<td>-4.6, -2.1§</td>
</tr>
<tr>
<td>Crs MOT, ml kPa⁻¹·kg⁻¹</td>
<td>13.4 (2.0)</td>
<td>14.4 (2.5)</td>
<td>13.0 (2.4)</td>
<td>-2.6, -0.3§</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence interval of mean difference; FRCpleth = functional residual capacity by plethysmography; Raw = airway resistance; Rrs = total respiratory resistance (single-breath technique); Crs = total respiratory compliance; SBT = single-breath technique; MOT = multiple occlusion technique. For definition of groups, see Table 1.

* Values are means with SD shown in parentheses.
† Group 3 compared with Group 2.
‡ p < 0.05.
§ p < 0.001.

(Groups 2 and 3 only), tidal volume, and peak tidal expiratory flow (PTEF) (Table 5). At any given lung volume, flows recorded after release of airway occlusions for the SBT were also significantly higher than those during tidal breathing (data not shown). When approximately 40% of tidal volume had been expired, the point at which analysis of the linear portion of the flow-volume curve normally commenced, flows were approximately 30% higher than the PTEF recorded in that infant during tidal breathing (ranging from 30% less to 115% greater). The mean flow recorded for each infant during the calculation of Rrs, which was used to denote the point of analysis for Raw, was equivalent to 72% (SD 13%) of PTEF during Raw measurements, a similar mean and range of percentages being obtained from all three groups of infants.

Repeat measurements of Crs and Rrs by the SBT while breathing warmed humidified air, as for the Raw measurements, were achieved in 18 infants: mean (SD) weight, 8.3 (2.5) kg; age range, 8 to 61 wk (Table 6). There was a significant increase in Crs during rebreathing, the mean increase (95% CI) being 193 (115, 283) ml/kPa (Figure 4). This was accompanied by a significant reduc-

![Figure 2](scatterplot_Rrs_initial_expiratory_Raw.png)

**Figure 2.** Scatter plot, according to the method of Bland and Altman (28), of the differences between total respiratory resistance and initial expiratory airway resistance and their mean. Open circles indicate Group 1 (healthy infants < 13 wk of age), open squares indicate Group 2 (healthy infants > 13 wk of age), open triangles indicate Group 3 (infants > 13 wk of age with prior wheeze who were asymptomatic when tested), closed triangles indicate Group 3 (infants who were symptomatic at testing).

![Figure 3](scatterplot_Rrs_end_expiratory_Raw.png)

**Figure 3.** Scatter plot, according to the method of Bland and Altman (28), of the differences between total respiratory resistance and end-expiratory airway resistance and their mean. Symbols as for Figure 2.
DISCUSSION

The results from this study indicate that, despite the apparent simplicity of the SBT for measuring $R_{rs}$, relative failure rate is higher than that encountered during plethysmographic measurements of $R_{aw}$ in the same infants. The failure rate for the SBT in the current study was considerably lower than that previously reported in preterm infants (13). This probably reflects fewer exclusions because of distortion of the flow-volume curve by excessive modulation of respiratory flow, which was noted in preterm neonates. Nevertheless, failure to achieve an adequate plateau or linearity of the flow-volume curve resulted in technical failures on 19% of occasions. Although the SBT did fail in two of the infants with the highest $R_{aw}$ values, there was no apparent relationship between failure rate and either symptoms or $R_{aw}$ values. This may reflect the fact that less than one third of the infants studied were symptomatic at testing.

Flow and Volume Dependency of Resistance

Airways resistance is known to be both flow- and volume-dependent, values tending to increase because of turbulence at higher flows and decrease because of increased elastic recoil and hence distention of the small airways at higher volumes (29-31). In addition, at any given lung volume or flow, $R_{aw}$ is generally lower during inspiration because of the distending influence of the negative inspiratory intrapleural pressure on intrathoracic structures. In adults and in healthy infants in whom the chest wall has begun to stiffen, such changes may be fairly minimal over the tidal range so that stable values of $R_{aw}$ are achieved. However, the highly compliant chest wall of young infants results in a low transpulmonary pressure at end-expiration (32), such that dynamic airway closure with marked elevation of end-expiratory resistance can occur within the tidal range. This tendency may be more pronounced in infants with airway disease caused by an increased pressure gradient along the airways in the presence of airway obstruction and/or the rise in intrapleural pressure that will accompany any active expiratory efforts. In adults, the stiffness of the bronchial wall protects the conducting airways from deformation and collapse because of positive intrathoracic pressures that develop during forced expiratory efforts. However, airways in immature animals are far more compliant than those in adults and hence vulnerable to collapse at smaller transmural pressures (33). Consequently, changes in lung volume that alter the interdependence between airways and parenchyma may act as a major determinant of airway caliber and resistance in infants. In this study, changes in $R_{aw}$ were found to occur throughout the expiratory range in all three groups of infants (Table 3). In this study, we attempted to minimize potential sources of variability when making comparisons between techniques by analyzing $R_{rs}$ and $R_{aw}$ at similar flows and phases of expiration. Because $R_{rs}$ is measured during passive expiration after an end-inspiratory occlusion, it may reflect the mechanics of the airways during initial expiration (together with a chest wall and tissue component) most closely (18). However, because analysis is performed on the descending portion of the flow-volume curve after peak expiratory flow has been attained, it could also reflect airway char-

### Table 4

<p>| Table 4 COMPARISON OF RESPIRATORY AND EXPIRATORY AIRWAY RESISTANCE (kPa·L⁻¹·s⁻¹) |</p>
<table>
<thead>
<tr>
<th>Mean Difference (SD)</th>
<th>95% Limits of Agreement</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{rs} - R_{aw}$ (initial expiration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1.98 (15.6)</td>
<td>-1.12, 5.12</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.29 (0.87)</td>
<td>-0.45, 3.03</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.97 (1.22)</td>
<td>-0.47, 4.41</td>
</tr>
<tr>
<td>$R_{rs} - R_{aw}$ (end-expiration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>0.68 (1.86)</td>
<td>-3.03, 4.40</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.55 (0.96)</td>
<td>-1.37, 2.47</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.31 (1.11)</td>
<td>-1.91, 2.54</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Table 1.

### Table 5

| Table 5 EFFECT OF REBREATHING ON TIDAL PARAMETERS |
|----------------------|--------------------------|--------------------------|
| GROUP 1, n = 42     | Baseline | Rebreathing | 95% CI* |
| $R_{rs}$, ml/min  | 45.6 | 46.6 | -0.9, 2.8 |
| $V_{t}$, ml        | 42.7 | 49.6 | 4.6, 9.2† |
| PTEF, ml/s         | 89.3 | 96.9 | 4.1, 16.9† |
| GROUP 2, n = 29     | Baseline | Rebreathing | 95% CI* |
| $R_{rs}$, ml/min  | 29.7 | 32.9 | 1.6, 4.7† |
| $V_{t}$, ml        | 106.6 | 136.5 | 23.5, 40.4‡ |
| PTEF, ml/s         | 137.4 | 182.6 | 31.5, 58.9‡ |
| GROUP 3, n = 36     | Baseline | Rebreathing | 95% CI* |
| $R_{rs}$, ml/min  | 32.7 | 36.5 | 2.6, 4.8† |
| $V_{t}$, ml        | 93.7 | 114.5 | 12.5, 28.9§ |
| PTEF, ml/s         | 138.0 | 173.3 | 24.6, 46.6† |

Definition of abbreviations: $RR$ = respiratory rate; $V_{t}$ = tidal volume; PTEF = peak tidal expiratory flow; Baseline = parameters measured without infants breathing room air; Rebreathing = parameters measured with infants rebreathing warmed, humidified, oxygen-enriched air. For definition of groups, see Table 1.

* Baseline values compared with Rebreathing values.
† $p < 0.05$
‡ $p < 0.01$
§ $p < 0.001$

### Table 6

| Table 6 EFFECT OF REBREATHING ON ASSESSMENT OF RESPIRATORY COMPLIANCE AND RESISTANCE BY THE SINGLE-BREATH TECHNIQUE |
|----------------------|--------------------------|--------------------------|
| Subjects (n)         | Baseline | Rebreathing | 95% CI* |
| $Cr_{rs}$, ml·kPa⁻¹  | 18     | 108.2 | 128.1 | 11.5, 28.3‡ |
| $R_{rs}$, kPa·L⁻¹·s⁻¹ | 18     | 4.20  | 3.30  | -1.45, -0.33† |
| Intercept, ml        | 18     | 19.3  | 31.2  | 4.7, 19.0‡ |

For definition of abbreviations, see Table 3.

* Baseline values compared with Rebreathing values.
† $p < 0.05$
‡ $p < 0.001$
characteristics toward end-expiration. Consequently, we compared Rs
with both initial and end-expiratory Raw. Raw was calculated at
the average flow recorded during Rs analysis in each infant, which
proved to be approximately 72% of PTEF, i.e., similar to Raw at
two-thirds PTEF, which has been conventionally calculated in the
past (25, 34). However, these attempts to match flows can at best
only be an approximation, with slight discrepancies being poten-
tially responsible for much of the observed variability.

Potential Influence of the Rebreathing Bag

Even when attempting to match flows and phase of respiration,
we could not control for the potential changes in resistance in-
duced by rebreathing warm humidified air. Adults are convention-
ally requested to pant during plethysmographic assessments of
Raw, both to minimize pressure changes caused by alterations
in temperature and humidity of respired gas and to keep the glot-
tis wide open, thereby minimizing upper airway resistance. Be-
cause infants cannot be asked to pant, they are allowed to re-
breathe warm humidified air, but this will inevitably result in some
build up of CO₂ and thereby increase ventilatory drive (Table 5).
This effect was less marked among Group 1 infants, reflecting
their smaller minute ventilation in relation to the volume within
the rebreathing bag.

It is not clear from the current study whether the reduction in
Rs that occurred when measurements were repeated during rebreathing (Figure 5 and Table 6) reflect a bronchodilator effect of CO₂ per se (35), increased tidal volume or increased dynamic elevation of lung volume subsequent to the increase in minute ventilation (i.e., volume dependence of R). The accompanying rise in Crs and volume intercept during rebreathing (Figure 4) sug-
gests that a change in lung volume may be a contributory factor.
If so, this has important implications with respect to timing of lung
volume measurements during plethysmography.

Influence of Changes in Gas Composition

During this study the pneumotachograph was calibrated with air,
which may have introduced a slight error into measurements dur-
ing the rebreathing of oxygen-enriched air (FiO₂ = 0.40). However,
such errors are likely to be small, and they would not account for
the differences reported in Table 6. Theoretically, Crs could be
overestimated and Rs underestimated by 11% if an infant breathed
100% O₂ through a pneumotachograph calibrated in air because
of the relatively high viscosity of O₂ compared with that in air (36,
37). However, this error falls to ≈ 2% at an FiO₂ of 0.4, and it would
be further compensated by the FiCO₂ of ≈ 0.06 commonly observed
in the bag during rebreathing since the viscosity of CO₂ is lower
than that of air.

It was not feasible to measure Rs under identical conditions
to Raw in all infants nor to repeat the MOT assessment of Crs
during rebreathing since this part of the study was attempted only
if infants remained asleep at the end of the main measurement
protocol. Furthermore, many infants failed to relax adequately un-
der conditions of stimulated breathing. Nevertheless, the observa-
tions in the subgroup of 18 infants emphasize the marked influence
of measurement conditions on measured values of respiratory
function and hence variability between techniques.

Partitioning of Respiratory System Resistance

Previous studies in which pulmonary and airway resistance have
been measured simultaneously and analyzed at identical flows
suggest that lung tissue resistance makes a relatively small
(< 15%) contribution to total pulmonary resistance (25, 38). This
may be related to the fact that the major component of lung tis-
sue resistance is thought to be due to hysteresis of the lung, which,
since it is inversely proportional to breathing frequency, will make
a smaller contribution in rapidly breathing infants than in adults.

The contribution of the chest wall is more controversial since
differences between techniques often preclude direct compari-
ions, whereas Raw reflects the dynamic changes that occur during Raw measurements, a linear flow-volume relationship was frequently obtained from infants with airway disease. Indeed, the failure rate of the SBT because of above, Rrs assesses expiratory resistance under passive conditions of the chest wall can be derived only when muscle activity is inhibited. In a comparative study of pulmonary and total respiratory resistance, Gerhardt and colleagues (9) found that Rrs was approximately 24% higher than pulmonary resistance (p < 0.001) in infants at approximately 1 yr of age. However, no significant difference was observed in preterm neonates, a finding that was attributed to the highly compliant chest wall in immature infants.

Within subjects in this study, Rrs was, on average, 80% greater than Raw during initial expiration and 27% greater than Raw during end-expiration in both groups of healthy infants, these values being 100 and 15%, respectively, among the wheezy infants. However, there was huge individual variability, and it is not meaningful to calculate a value for tissue resistance or visco-elasticity simply as the difference between the two techniques.

Passive versus Dynamic Resistance

In addition to differences in measurement conditions discussed above, Rrs assesses expiratory resistance under passive conditions, whereas Raw reflects the dynamic changes that occur during tidal breathing. Despite obvious nonlinearities of the pressure-flow loop during Raw measurements, a linear flow-volume relationship was frequently obtained from infants with airway disease (Figures 6 and 7). Indeed, the failure rate of the SBT because of nonlinearity was greater in the group with prior wheeze than in the mixed population and that end-expiratory Raw was significantly greater than Rrs among the wheezy infants, many of whom were symptomatic at the time of testing.

When using the SBT, time is allowed during the end-inspiratory occlusion for relaxation of the diaphragm and other inspiratory muscles. It could therefore be argued that the level of activity of the inspiratory and laryngeal expiratory muscles during analysis of the passive flow-volume curve most closely resembles that occurring at midexpiration during tidal breathing and that Rrs should therefore be compared with midexpiratory Raw. Although we did consider this approach, the higher flows occurring towards midexpiration were associated with increased values for Raw, presumably because of increased turbulence (25), and therefore tended to increase rather than diminish any discrepancies between Raw and Rrs.

Validity of the SBT

Concern has been expressed regarding the use of the SBT in intubated infants because of possible laryngeal modulation of expiratory airflow resulting in a falsely elevated volume intercept and hence Crs and Rrs (13, 14, 27). Similar findings were recently reported by Springer and colleagues (18). This group found virtually identical values of weight-corrected FRCpleth in 15 “normal” and in nine postbronchiolitic infants as in the current Groups 2 and 3 (healthy > 13 wk and prior wheeze, respectively). Springer and colleagues did not tabulate absolute values of Rrs and Raw, making direct comparisons difficult, but their published illustrations reveal that initial expiratory Raw was equal to or exceeded Rrs in approximately one third of the mixed population and that end-expiratory Raw was significantly greater than Rrs among the wheezy infants, many of whom were symptomatic at the time of testing.

Within subjects in this study, Rrs was, on average, 80% greater than Raw during initial expiration and 27% greater than Raw during end-expiration in both groups of healthy infants, these values being 100 and 15%, respectively, among the wheezy infants. However, there was huge individual variability, and it is not meaningful to calculate a value for tissue resistance or visco-elasticity simply as the difference between the two techniques.

Passive versus Dynamic Resistance

In addition to differences in measurement conditions discussed above, Rrs assesses expiratory resistance under passive conditions, whereas Raw reflects the dynamic changes that occur during tidal breathing. Despite obvious nonlinearities of the pressure-flow loop during Raw measurements, a linear flow-volume relationship was frequently obtained from infants with airway disease (Figures 6 and 7). Indeed, the failure rate of the SBT because of nonlinearity was greater in the group with prior wheeze than in the group of healthy infants of a similar age. After end-inspiratory occlusions, infants frequently inspire earlier than usual on the subsequent breath, such that any rise in end-expiratory resistance caused by dynamic airway closure may be missed. Furthermore, analysis of the “passive” time constant is limited to the “linear” portion of the flow volume curve, when any muscle activity has supposedly been inhibited; consequently, measurements of Rrs may reflect the dimensions of the airways under passive conditions, but they cannot reflect the dynamic changes that normally occur throughout the breath. This would explain why values of end-expiratory Raw exceeded those of Rrs in approximately 25% of infants studied.

Similar findings were recently reported by Springer and colleagues (18). This group found virtually identical values of weight-corrected FRCpleth in 15 “normal” and in nine postbronchiolitic infants as in the current Groups 2 and 3 (healthy > 13 wk and prior wheeze, respectively). Springer and colleagues did not tabulate absolute values of Rrs and Raw, making direct comparisons difficult, but their published illustrations reveal that initial expiratory Raw was equal to or exceeded Rrs in approximately one third of the mixed population and that end-expiratory Raw was significantly greater than Rrs among the wheezy infants, many of whom were symptomatic at the time of testing.
Conclusions
Despite the difficulties in interpreting results from individual infants and the relatively high failure rate, the SBT was simple to use and is potentially far more applicable than plethysmography, which is essentially limited to specialized laboratories and generally unsuitable for critically ill infants. Although it has been suggested that Rs may reflect initial expiratory airway mechanics, this is still open to debate. In this study both Rs and end-expiratory Raw were significantly higher in infants with prior wheeze, most of whom were asymptomatic at time of testing, than in healthy infants of similar age and weight. This suggests that measurements of Rs may be of value in epidemiologic studies, although further work is needed to define the extent to which elevated values of Rs correctly identify those infants with airflow obstruction as determined by clinical symptoms or other objective measures of airway function. However, the clinical value of measurements of Rs within individual infants may be limited by its failure to detect the dynamic changes in resistance throughout the breath that are clearly evident during plethysmographic studies.

Acknowledgment: The writers gratefully acknowledge the cooperation of the parents of infants who participated in this study; the support of pediatricians at the Hospital for Sick Children and the Queen Elizabeth Hospital for Sick Children, Hackney, who referred infants under their care; the cooperation of the general practitioners and health visitors at Chirsp Street and St. Stephen's Health Centres for permission to contact families of healthy infants; Helena Wagstaff and Liane Pilgrim who assisted with recruiting healthy infants; and the secretarial support provided by Jo Turner.

References
In Vitro Assessment of Infant Pulmonary Function Equipment

Elizabeth A. Jackson, FRCA, Allan L. Coates, MD, Monika Gappa, MD, and Janet Stocks, PhD

Summary. Commercially available automated pulmonary monitors are used increasingly in neonatal intensive care units. However, detailed information regarding the static and dynamic accuracy of these monitors is rarely available. Collaboration between scientists, clinicians, and manufacturers is essential to establish improved technical standards and protocols for testing of equipment and for the development of more reliable neonatal pulmonary monitors. The aim of this study was to develop a protocol for the in vitro assessment of commercial infant pulmonary function equipment which could be applied within the laboratory to provide rapid feedback to the manufacturer. A recently released neonatal pulmonary monitor, the Bicore CP100 (software version 3.3), was selected for the development of this protocol. The deadspace and resistance of the measuring device were determined. The flow and airway pressure measuring systems were evaluated alone and connected to a tracheal tube for both static accuracy and frequency response. The pressure–volume relationship of the esophageal balloon was determined and its static accuracy and frequency response were assessed. The algorithms for on-line calculations were checked and their correct application confirmed by examination of an ASCII data print out. Finally, the pulmonary monitor was tested during intermittent positive pressure ventilation of a neonatal lung model of known compliance and resistance. Pediatr Pulmonol. 1995; 19:205-213. © 1995 Wiley-Liss, Inc.

Key words: Infant, pulmonary function monitor, equipment assessment.

INTRODUCTION

Continuous monitoring techniques to guide ventilation of the sick neonate are used more widely and are becoming more complex. Initial interest was in transcutaneous oxygen and carbon dioxide monitors and devices are now available to monitor respiratory and lung mechanics. The American Thoracic Society has established technical standards and testing procedures to ensure that equipment used for spirometric measurements in older subjects is capable of providing a reasonable level of accuracy. Such standards do not exist for neonatal monitoring equipment, and the manufacturers' assessment of equipment prior to marketing is frequently either less extensive than might be desired or the technical detail to attest to the accuracy of the equipment is unavailable. There are a number of potential sources of errors in equipment. The commonest ones are that the actual measuring device does not have a predictable output for a known input over the full range of flow and pressure seen in clinical practice (inaccurate calibration), the frequency response of the equipment is inadequate to follow a rapidly changing signal, and the computer algorithms used in calculating results are either incorrect or not applicable to the situation in question.

The aim of this study was to develop a laboratory protocol to evaluate the static and dynamic accuracy of

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neonatal pulmonary monitors. The protocol aimed to (1) assess the static accuracy and frequency response of the measuring devices incorporated in a pulmonary function monitor (flow, airway and esophageal pressures) both alone and assembled as intended for use with a tracheal tube, (2) assess the application of computer algorithms for on-line calculation of mechanics, and (3) evaluate the apparatus during intermittent positive pressure ventilation (IPPV) of a neonatal lung model. A recently released monitor, the Bicore CP100 Neonatal Pulmonary Monitor, was selected to establish this protocol.

MATERIALS AND METHODS

The Bicore CP100 (software version 3.3) (Bicore Monitoring Systems, Irvine, CA) consists of a disposable, precalibrated, low dead space, variable orifice pneumotachograph (PNT) with a pressure port on each side of the variable orifice, so that both the differential pressure across the screen and the pressure at the airway opening (Pao) can be measured with two transducers. Each pressure port is attached to the monitor by a 1.13 m length of 2 mm internal diameter (i.d.) tubing. The PNT is compatible with standard 15-mm tracheal tube connectors. The PNT has an effective dead space of less than 1 mL and a working range of 0–500 mL s⁻¹. A disposable occlusion valve that connects between the PNT and the ventilator circuit is also available.

Esophageal pressure (Pes) is measured using a disposable 25 mm balloon mounted on a stiff 30 cm tube of 1.1 mm i.d.. This is connected to the monitor by a 1.22 m length of stiff tubing of 1.3 mm i.d. The coefficient of displacement of the transducer is 0.022 mL kPa⁻¹ (manufacturer’s data). The balloon is also factory calibrated and the degree of inflation is computer controlled with the operator having a choice between 5 unspecified filling volumes.

Flow and pressures are sampled at 100 Hz. The Bicore displays values for respiratory rate, inspired and expired tidal volumes, peak inspiratory and expiratory flows, inspiratory and expiratory times, % tube leak, and expired minute volume. Values are given for both ventilator and spontaneous breaths. For the ventilator breaths alone, total respiratory dynamic compliance (Cdyn) and resistance (Rdyn), and dynamic compliance over the terminal 20% of inspiration as a ratio of compliance over the whole breath (C20/Cdyn)³ are displayed. Pressures are given in cm H₂O. There is a choice of averaging over 1, 10, or 30 breaths. In addition, when the esophageal balloon is in use, transpulmonary pressure is calculated as the difference between Pes and Pao and values for lung mechanics are displayed. The occlusion valve is intended for the measurement of passive respiratory mechanics during spontaneous and ventilator breaths.

The flow, Pao, and Pes measuring devices were evaluated for static measurement accuracy and frequency response. The resistance of the PNT, both alone and when connected to the occlusion valve, was determined. Then, using a neonatal lung model, the values of tidal breathing parameters displayed by the Bicore CP100 were compared to those calculated independently from the Bicore ASCII data printout using the algorithms provided by the manufacturer. The algorithms used for calculation of respiratory parameters were examined to check whether they were appropriate. Finally, the values displayed by the Bicore CP100 during ventilation of the lung model were compared to reference values from a Fleisch PNT and Validyne transducers with known frequency responses.⁴

Assessment of Flow Measuring Apparatus

The effective deadspace was taken as the increase in deadspace resulting from the insertion of the PNT, alone or in combination with the occlusion valve, between a Portex 15-mm tracheal tube connector and 15-mm Portex right angled connector, each measured by water displacement. The accuracy of the PNT was evaluated under three conditions: first, connected to a 13 cm long 3.5 mm Portex tracheal tube with a 15 mm connector attached to a Portex right angled connector; second, with a 13 cm long 3.0 mm Portex tracheal tube with the same connector without endotracheal tube, and finally with a 10 cm length of 15 mm i.d. tubing connected to each side of the PNT. Flows of air from 0 to 500 mL s⁻¹ were passed through the PNT, using calibrated rotameters (KDG 1100, Burgess Hill, Sussex, England). A 1–15 L min⁻¹ rotometer was used for flows up to and including 200 mL s⁻¹ and a 4–40 L min⁻¹ rotometer from 200 to 500 mL s⁻¹. The rotameters had been calibrated at 15°C and 760 mm Hg. The atmospheric pressure at the time of testing was 746 mm Hg and the room temperature was 24°C, although the temperature of the air coming out of the wall outlets was cooler than this. The equipment was evaluated bidirectionally under all three conditions. The actual flow from the rotometer was compared to the digitized flow of the Bicore CP100 displayed as an ASCII output on a personal computer, using software supplied with the Bicore monitor.

The resistance of the PNT was assessed bidirectionally using known flows of air from the calibrated rotameters and measuring the pressure drop across the apparatus with a Validyne MP45 ± 50 cm H₂O pressure transducer. The output of the transducer was digitized at 200 Hz, using an Analog Devices A-D converter, and data was collected on an IBM compatible 386 personal computer using RASP software (Respiratory Analysis Program, Physio Logic, Newbury, England). Calibration of the pressure transducer was performed with a water manometer.
The frequency response of the PNT alone and attached to the 3.5 mm i.d. tracheal tube was assessed, using the pressure chamber method described by Vallinis et al. Briefly, the apparatus consists of an airtight 81-L rectangular box separated in the middle by an acoustic suspension loudspeaker, the membrane of which had been sealed with latex. The test apparatus and a reference transducer (Validyne MP45 ± 7 cm H₂O) are connected directly to the side of the chamber which faces the front of the speaker using a widebore connector. The frequency response of the reference transducer has been shown to be excellent in amplitude and phase to at least 40 Hz. The loudspeaker is driven by a sinusoidal wave form produced by a signal generator (Brookdeal Signal Source Type 471) interfaced to a low-frequency power amplifier to generate sinusoidal pressure changes within the box. The volume displaced by the speaker movement is in the order of 700 mL per cycle. The volume of air entering and leaving the chamber when the test apparatus is a PNT is negligible in comparison to the displacement volume, so that there is no distortion of the sinusoidal pressure wave form. The flow through the PNT is directly proportional to the pressure within the chamber. The amplifier was adjusted to keep the reference transducer pressure constant, which gave peak flows through the PNT of = 130 mL s⁻¹, which in turn was within the manufacturer's stated working range. The direct current voltage outputs of both the test apparatus and reference transducers were displayed on the X and Y axes, respectively, of a memory oscilloscope (Tektronix Model 5223) to produce Lissajous loops. With a frequency of 1 Hz from the signal generator, the gain of the reference transducer was adjusted so that the peak to trough voltage outputs of the test and reference devices were equal. The frequency was then increased by 1 Hz steps to 10 Hz. The attenuation and phase lag were calculated using previously described methods as shown in Figure 1.

**Fig. 1. Calculation of attenuation and phase angle from the Lissajous loop.** The signal from the reference transducer (ref.) is plotted on the Y axis and that from the transducer being tested (test) on the X axis. Reproduced with permission from Vallinis et al.

**Assessment of Airway Pressure Measuring Apparatus**

The accuracy of the airway pressure measuring apparatus was established by applying known pressures over the range of −25 to +50 cm H₂O, using a water manometer and comparing these with the Bicore measurement displayed as an ASCII output. The frequency response of the Pao measurement device was assessed in an analogous way to that used for the flow measuring apparatus.

**Assessment of Esophageal Pressure Measuring Apparatus**

Two balloon designs were assessed, the second being a manufacturer's new release in response to feedback from the assessment of the original balloon. The pressure volume characteristics of the esophageal balloon were established according to the technique described by Beardsmore et al. Briefly, the balloon was submerged in water to a depth of 5 cm H₂O to empty it of air. It was then attached to a 1-mL syringe and the balloon was withdrawn from the water. Small (0.05 mL) increments of air were then added and the resulting pressure measured using a Validyne MP45 ± 2 cm H₂O transducer previously calibrated with a slanting oil manometer (Poddy meter). The pressure volume characteristics of the balloon were plotted, and the region where there was no significant change in pressure (i.e. <0.05 kPa) with change in volume, the "working range of the balloon," was thus identified.

The Bicore CP100 uses automated balloon filling, giving the operator a choice of 5 different unspecified levels of filling. For each filling level the accuracy of the system was assessed by placing the balloon in a closed container that could be pressurized. The pressure in the chamber was varied between ±30 cm H₂O and measured with a water manometer. This applied pressure was compared to the esophageal balloon pressure measurement using the Bicore CP100 ASCII data display. The frequency response of the esophageal pressure measuring apparatus was determined as described for the flow measuring apparatus.

**Assessment of Algorithms and On-Line Calculation of Dynamic Respiratory Parameters**

The algorithms used by the Bicore CP100, as described by the manufacturer, were compared with those in common use for research measurements. An ASCII data print out of flow and airway pressure during mechan-
ica! ventilation of an SLE (Specialised Laboratory Equipment Ltd, South Croydon, Surrey, UK) neonatal lung simulator was obtained and used to calculate the dynamic respiratory parameters displayed by the Bicore, using the formulas provided by the manufacturer. The lung model compliance was set at 3 mL cm H2O⁻¹ and resistance at 100 cm H2O L⁻¹ s. The SLE neonatal ventilator set at a respiratory rate of 25 min⁻¹ and peak pressure of 20 cm H2O. The PNT was connected directly to the 15-mm port of the lung simulator. The calculated values of a selection of the dynamic respiratory parameters were compared with those displayed by the Bicore CP100 to check that the algorithms were being applied as stated. Application of algorithms for esophageal manometry was not assessed as this would have required in vivo data collection which was beyond the scope of the present study.

Assessment of Dynamic Mechanics Measurements Using a Neonatal Lung Simulator

The Bicore CP100 was attached via a 3.0 mm Portex tracheal tube to an SLE neonatal lung simulator, which is based on the ISO (International Standards Organisation) design and consists of an isothermal compliance chamber and linear resistance. The lung model was ventilated (1) by hand, using a Portex 15 mm disposable T-piece to generate a near sinusoidal respiratory flow pattern (Fig. 2A) at a rate of 50 and 100 per minute, and (2) with a Siemens Servo 900C ventilator with similar respiratory frequencies and tidal volumes, but a more complex waveform (Fig. 2B). A Fleisch 0 PNT was attached in series, proximal to the PNT of the Bicore CP100, and a pressure port was attached at the tracheal tube connection. Validyne differential pressure transducers were used to measure flow and airway pressure. The Fleisch PNT was calibrated, using known flows of air from calibrated rotameters, and the airway pressure transducer was calibrated with a water manometer. The unfiltered outputs of the Validyne transducers were digitized at 200 Hz, using an Analog Devices A-D convertor and data collected on a personal computer, using RASP software. Flow was digitally integrated to volume. The Fleisch PNT attached to a 3.0 mm i.d. tracheal tube has been shown to have a flat frequency response to 20 Hz. The values for Rdyn and Cdyn were calculated, using the Mead-Whittenberger analysis adapted for neonates. The lung model was set to a compliance of 1.0 mL cm H2O⁻¹ and resistance of 200 cm H2O L⁻¹ s. The values for Rdyn and Cdyn given by the Bicore CP100 were compared with those set on the test lung and to those calculated from the data collected, using the Fleisch PNT.

RESULTS

Assessment of Flow Measuring Apparatus

The effective deadspace of the PNT alone and connected to the occlusion valve was 1.0 and 1.6 mL, respectively. The static accuracy of the PNT alone and attached to 3.0 and 3.5 mm i.d. tracheal tubes over the range ±500 mL s⁻¹ is shown in Figure 3. A -ve or +ve sign is used to denote flows applied in the expiratory or inspiratory direction, respectively. The accuracy was better for the PNT alone with measurements within 5% from -400 to +450 mL s⁻¹; attaching a tracheal tube reduced the range over which 5% accuracy was achieved to -200 to +300 mL s⁻¹.

The pressure drop across the PNT at flows of 0 to 500 mL s⁻¹ in both the inspiratory and expiratory directions were as shown in Figure 4. The resistance of the PNT was 1.5 kPa L s⁻¹ at 100 mL s⁻¹ and remained similar across the tested flow range. Attachment of the Bicore dispos-
Assessing Neonatal Pulmonary Monitors  

![Image of a graph showing flow vs. known flow for Bicore CP100 with and without tracheal tubes.](image)

**Fig. 3.** Known flow plotted against the flow measurements of the Bicore CP100 for the PNT alone and attached to 3.0 and 3.5 mm i.d. tracheal tubes. The dashed line is the line of identity. Inspiratory flows are positive and expiratory flows negative.

![Image of a graph showing pressure drop vs. flow for Bicore PNT.](image)

**Fig. 4.** Steady-state pressure drop across the Bicore PNT alone and attached to the occlusion valve during known inspiratory and expiratory flows.

able occlusion valve caused no significant change in resistance at flows below 200 mL s\(^{-1}\), but had an increasing influence at higher flows (Fig. 4).

Modified Bode plots of the frequency response of the flow transducer, where phase shift and attenuation (not as a logarithm) are plotted against the logarithm of frequency,\(^2\) are shown in Figure 5. This was performed for the PNT alone and when attached to a 3.5 mm i.d. tracheal tube. The frequency response in terms of both attenuation and phase angle was degraded considerably by the addition of the tracheal tube.

**Assessment of Airway Pressure Measuring Apparatus**

The known pressure and measured pressure were within 5% over the tested range of -25 to +50 cm H\(_2\)O. Modified Bode plots of the frequency response are shown in Figure 6. The frequency response was good to at least 10 Hz and considerably better than for the PNT.

**Assessment of the Esophageal Pressure Measuring Apparatus**

Pressure-volume curves for the original and manufacturer's modified balloons are shown in Figure 7. The near vertical portions of the curves represent the "working range" of the balloon, which for the original balloon was very limited (0.15 mL), but for the modified balloon was much improved (0.30 mL). The original balloon had poor static accuracy at all filling levels (data not shown). However, frequency response was good to at least 10 Hz. The static accuracy of the modified balloon at each of the 5 computer-controlled filling levels is shown in Figure 8. Filling level 3 produced the best results with static accuracy within 5% over the range -30 to +30 cm H\(_2\)O.

**Assessment of Algorithms and On-Line Calculation of Dynamic Respiratory Parameters**

Appropriate algorithms were used for the calculation of tidal breathing parameters. The dynamic respiratory mechanics measurements were based on the Mead and Whittenberger method of analysis\(^1\) and the calculation of dynamic lung compliance on multiple linear regression...
as described by Bhutani et al.\textsuperscript{12} The parameter $\frac{C_{20}}{C_{\text{dy}}}^{\text{dy}}$, which was also displayed, was calculated using an algorithm based on the work of Fisher et al.\textsuperscript{3} Unfortunately, it is not clear from the original description how the parameter should be calculated during certain patterns of ventilation. The algorithm used for calculation of occlusion mechanics was not well recognized and not based on the single breath technique as described by LeSouef et al.\textsuperscript{13}

Table 1 shows the tidal breathing parameters during mechanical ventilation of the lung model with an SLE neonatal ventilator. There was good agreement between values displayed by the Bicore CP100 and those calculated by applying the Bicore CP100 algorithms to a printout of ASCII flow and airway pressure data from the Bicore CP100. Both sets of values represent the mean of 10 breaths.

Assessment of Dynamic Mechanics Measurements Using a Neonatal Lung Simulator

During ventilation of the neonatal lung model with both a simple and complex waveform (Fig. 2), the Bicore CP100 and the Fleisch PNT with Validyne transducers both gave values for $C_{\text{dy}}$ and $R_{\text{dy}}$ within 20% of the set values (Table 2). However, the Bicore CP100 gave values that were always lower than the values obtained with the Fleisch.

**DISCUSSION**

Until recently the complexity of the measuring equipment and time-consuming nature of the analysis of results have limited the use of infant pulmonary function testing to research establishments with highly trained personnel. During the past 5 years several commercially available systems for automated measurements of infant pulmonary function have become available. These automated monitoring systems are used increasingly in neonatal intensive care by clinicians with little formal training in the assessment of neonatal pulmonary function. It is important that equipment has characteristics adequate to ensure accurate and reliable results when used for clinical monitoring purposes. However, reliable technical data concerning the accuracy of the equipment under dynamic conditions, when attached to the connector (i.e., tracheal tube) that will be used during clinical use, are rarely available.

Evaluation of new equipment should involve both in vitro and in vivo assessments. This study was designed to develop a protocol for the in vitro evaluation of new commercially available neonatal pulmonary monitors. In vitro assessment allows the rapid identification of hardware and software problems that will preclude satisfactory function of a pulmonary monitor. However, in vivo studies are also necessary as the effect of patient respiratory effort, the interaction of the patient with synchronized forms of respiratory support, and the influence of tracheal tube leaks cannot be adequately assessed in the laboratory. In addition, any practical difficulties in connecting and positioning the measuring devices and the extent to which such devices are tolerated by infants require in vivo assessment. Quality criteria for acceptance of technically satisfactory measurements also have to be developed in the clinical setting.

Measurements of the static accuracy of the flow measuring apparatus demonstrate the importance of assessing the apparatus bidirectionally and while attached to a tracheal tube. The working range of the flow measuring apparatus was considerably reduced by the addition of a tracheal tube, with subsequent underestimation of expiratory flows greater than 200 mL s\textsuperscript{-1} and overestimation of inspiratory flows greater than 300 mL s\textsuperscript{-1}. Although this was considerably less than the manufacturer's stated working range, it is adequate for measurements in intubated and ventilated neonates. In clinical practice, flows up to 500 mL s\textsuperscript{-1} would only be expected in patients with tracheal tubes larger than those used in our study. Measurements were not repeated with larger tracheal tubes as the manufacturer was planning the release of a new PNT
Assessing Neonatal Pulmonary Monitors

0.6

0.4

0.2

0.0

Pressure kPa

Volume

ml

0.6

0.4

0.2

0.0

-0.2

0.0

0.2

0.4

0.6

0.8

A

B

Fig. 7. Pressure-volume characteristics of Bicore CP100 esophageal balloons. (A) Original balloon, (B) modified balloon.

![Graph](image)

Fig. 8. Static accuracy of the modified Bicore CP100 esophageal balloon at the five different computer-controlled filling levels. The dashed line is the line of identity.

### TABLE 1—A Comparison of Displayed and Calculated Respiratory Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bicore CP100 values</th>
<th>Calculated values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Inspired tidal volume (mL)</td>
<td>40.4</td>
<td>40.0</td>
</tr>
<tr>
<td>Expired tidal volume (mL)</td>
<td>39.5</td>
<td>39.7</td>
</tr>
<tr>
<td>% leak</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Inspiratory time(s)</td>
<td>0.78</td>
<td>0.78</td>
</tr>
<tr>
<td>Expiratory time(s)</td>
<td>1.47</td>
<td>1.48</td>
</tr>
<tr>
<td>Mean airway pressure (cm H₂O)</td>
<td>11.1</td>
<td>11.1</td>
</tr>
<tr>
<td>Peak airway pressure (cm H₂O)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Peak inspiratory flow (mL s⁻¹)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Peak expiratory flow (mL s⁻¹)</td>
<td>73</td>
<td>73</td>
</tr>
</tbody>
</table>

*The calculated values have been obtained by applying the algorithms given by the manufacturer to an ASCII data printout from the Bicore CP100 during ventilation of a lung model.

The frequency response of the flow measuring apparatus was also considerably degraded by the addition of a tracheal tube. The degradation in the performance of the PNT by the addition of a tracheal tube is not a phenomenon peculiar to the Bicore PNT. The linearity of both Fleisch and screen type PNTs, which, like the Bicore variable orifice PNT, depends on the measurement of a pressure drop across a resistance, has been shown to be altered by changes to the geometry of any attached tubing, particularly with respect to sudden changes in diameter. Such changes can result in turbulence at flows that were previously laminar and alterations in the velocity profile of the gas, such that a greater or lesser proportion of the faster moving molecules is directed close to the points where the differential pressure is measured. The effects of gas composition, humidity, and temperature on the static accuracy of the Bicore PNT were not assessed, but could be included in the protocol. Conversion factors for gases other than air are supplied by the manufacturer. However, as oxygen enriched air is frequently used during IPPV a correction for FiO₂ should ideally be incorporated with the monitor.

Assessment of the airway pressure measuring apparatus showed a static accuracy within 5% and flat frequency response to 10 Hz. This is clearly acceptable and was significantly better than for the flow measuring apparatus. The frequency response of the flow and pressure measuring devices will be partly determined by the char-
TABLE 2—Simultaneous Values of $C_{dyn}$ and $R_{dyn}$ Obtained Using the Bicore CP100 and the Fleisch PNT With Validyne Transducers, During Intermittent Positive Pressure Ventilation (IPPV) of a Neonatal Lung Model With a Set Compliance of 1.0 mL cm H$_2$O$^{-1}$ and Resistance of 200 cm H$_2$O L$^{-1}$ s

<table>
<thead>
<tr>
<th>Mode of IPPV</th>
<th>Respiratory rate min$^{-1}$</th>
<th>$C_{dyn}$ (mL cm H$_2$O$^{-1}$)</th>
<th>$R_{dyn}$ (cm H$_2$O L$^{-1}$ s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td></td>
<td>Bicore</td>
<td>Fleisch</td>
</tr>
<tr>
<td>Hand</td>
<td>50</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Hand</td>
<td>100</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Servo 900C</td>
<td>50</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Servo 900C</td>
<td>100</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

characteristics of the transducer tubing.$^6,16$ Stiff fine bore tubing as used in the Bicore CP100 appears to be satisfactory.

The original version of the Bicore CP100 neonatal esophageal balloon had a very limited working range. In response to feedback from this study, the manufacturer released a modified version with a larger working range and hence adequate static accuracy. An "occlusion test"$^{17,18}$ would be necessary to ensure that the balloon was functioning satisfactorily in vivo. Although, an "occlusion test" could be performed in theory, it was not possible at the time of assessment to display the esophageal pressure and airway pressure either as an X-Y plot or as superimposed time based traces to ensure that the conditions for accuracy had been met.$^{19}$

Well described algorithms had been chosen for calculation of tidal breathing parameters and dynamic respiratory and lung mechanics. The method used for calculating dynamic respiratory mechanics is based on identifying points of zero flow at the transitions between inspiration and expiration when airway pressure is changing very rapidly (Fig. 2). The Bicore algorithm incorporates linear interpolation of the airway pressure and flow samples at these transitions which should improve accuracy. However, multiple linear regression$^{12}$ which is not dependent on identifying points of zero flow may be a better method of calculating dynamic respiratory mechanics during IPPV. The method of calculating mechanics from occlusion data was unusual and inappropriate. It failed to allow for any dynamic elevation of lung volume in spontaneously breathing infants, or to be applicable to ventilated infants receiving synchronized respiratory support.

The assessment of the on-line calculation of tidal breathing parameters showed that the algorithms were applied as stated by the manufacturer. Other algorithms were not checked as they were under constant review by the manufacturer, and the purpose of this study was not to validate the Bicore CP100, but to establish that such validation is feasible.

In the preliminary assessment of the Bicore CP100 during ventilation of the neonatal lung model of known compliance and resistance, mechanics values within 20% of the set values were obtained, even when a mechanical ventilator was used with a high respiratory frequency and complex waveform. The use of more appropriate algorithms, based on multiple linear regression, may have given better results. Obtaining measurements during ventilation of a lung model was quick and simple and did not require access to ASCII or analog outputs from the monitor. This method of assessment is therefore applicable even to monitors that do not incorporate facilities for accessing digital and analog raw data. Ideally this part of the protocol should be further developed to include assessment using multiple lung models with a wide range of mechanical properties. This approach would be similar to that used for assessing spirometric equipment for use in adults,$^1$ which involves applying a series of known test waveforms to the spirometer.

This study demonstrates the kind of assessments necessary whenever clinicians, scientists, and manufacturers wish to improve standards of accuracy for neonatal pulmonary monitors. The response of the manufacturers has resulted in much of the numerical data presented here for illustrative purposes becoming outdated before publication. A committee of experts that can respond rapidly to the needs of manufacturers and scientists in developing standards for the performance and assessment of both the hardware and software incorporated in neonatal pulmonary monitors may be required. In setting standards a balance will be necessary between accuracy, ease of use, and cost. It is possible that the level of accuracy required for clinical monitoring to permit optimization of ventilator therapy is generally less than that required for research studies involving mechanics measurements, although extreme accuracy may be important in certain infants.$^{20}$ However, the level of accuracy of any given monitor in a wide range of clinical situations should be known, so that the potential limitations of the results are fully appreciated.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of Bicore Monitoring Systems, who provided technical advice that allowed access to the analog data signals and ASCII data output as well as the loan of the Bicore CP100 monitor.
The equipment for the determination of frequency response was loaned by the Department of Biomedical Engineering, The Hospitals for Sick Children, London.

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A New Microtransducer Catheter for Measuring Esophageal Pressure in Infants

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Summary. Measurement of esophageal pressure, as a reflection of pleural pressure, is essential for assessment of dynamic lung mechanics in neonates and infants. Conventionally, an esophageal balloon or a fluid-filled catheter is used, but considerable skill is required to obtain accurate results. Both devices have problems, and failure to achieve valid occlusion tests have been reported, particularly in small infants with lung disease. Recently, a flexible #3 French gauge (FG) microtransducer catheter (MTC®, Dräger Netherlands) has become available for medical monitoring. We have assessed the accuracy and feasibility of using this device for measuring lung mechanics in 51 spontaneously breathing infants and small children aged 1 day to 24 months (weight 1.35 to 12.0 kg), 9 of whom were healthy neonates, the remainder suffering from a variety of cardio-respiratory diseases, and in 18 sick ventilated infants (weight 0.6 to 4.0 kg). Positioning of the catheter was well tolerated by all infants. The ratio of esophageal to airway opening pressure changes (ΔPes/ΔPao) ranged from 0.94 to 1.09 [mean (SD) 1.013 (0.03)] for the spontaneously breathing infants and from 0.98 to 1.06 [mean (SD) 1.003 (0.02)] in the ventilated infants with no significant difference in this ratio between the two groups (p = 0.16). This new generation of catheter tip pressure transducers may provide a simpler and more reliable tool for assessing transpulmonary pressure changes in infants than has previously been available.

Key words: Dynamic lung mechanics, microtransducer catheter, infant respiratory function tests, esophageal manometry.

INTRODUCTION

Measurements of dynamic lung mechanics have been performed in infants for over 40 years1-3 and have been used to assess growth and development of the lung, determine severity and progression of disease and evaluate response to therapy. The small preterm neonate is at high risk of developing chronic lung disease, which is thought to be a consequence of both prematurity and respiratory support with positive-pressure ventilation and high inspired oxygen concentrations. Measurements of pulmonary function during the course of the disease have contributed to an improved understanding of the natural history of disease, the development of new treatment strategies, and the reduction in complications during mechanical ventilation.2-4 However, there is still a lack of easily applicable and valid techniques for use in infants with respiratory disease.

Flow, volume, and Ptp are necessary for calculation of pulmonary mechanics. Ptp, the driving pressure of the respiratory system, is the difference between Pao and Ppl. Because Ppl is not readily accessible in human studies, it is usually measured indirectly as Pes. During the 1980s work was performed to improve the accuracy of Pes recordings, including the recommendation that the validity of these measurements should be verified by performing an occlusion test.5-10 In the absence of airflow during an airway occlusion, pressures should equilibrate within the respiratory system and hence be reflected at the airway opening. During respiratory efforts against an airway occlusion, ΔPao should equal ΔPpl. Thus, if ΔPes equals ΔPao, it can be assumed that ΔPes is reflecting...
ΔPpl accurately and may be used to calculate dynamic lung mechanics.11-13

Three different techniques for measurement of Pes have been described for use in infants: Esophageal balloon manometry,1 fluid-filled catheter manometry,10,14 and micromanometry.15 Successful applications of either esophageal balloon or fluid-filled catheter manometry in healthy infants have been reported, but problems occurred when esophageal manometry was used in small, sick infants.16-18 The liquid-filled catheter has been applied more successfully in this group.10,14 Using a fluid-filled catheter, Neto and coworkers19 obtained valid occlusion tests in 14 spontaneously breathing preterm infants, even in the presence of marked chest wall distortion. However, the liquid-filled catheter system has to be flushed with sterile water or normal saline at regular intervals to keep the system free of air-bubbles, which, together with the skill required to obtain accurate recordings, has prevented this technique being used routinely for lung function assessment in small sick patients. Recently, the use of an air-filled catheter for esophageal manometry has been described in adults (20), but this has not yet been evaluated in infants.

Attempts to use a catheter-tip pressure transducer during the 1980s proved disappointing, since the device tended to overread when in situ and did not have any advantages when compared to catheters with attached balloons or fluid filled catheters (15). Because of the listed problems, there has been a decline in the popularity of esophageal manometry in recent years. However, because of the potential advantages of a catheter-tip manometer which records dynamic pressure changes throughout the breathing cycle, the minimal apparatus dead space compared to many other techniques of measuring respiratory mechanics in infants and the rapidity with which lung mechanics may be assessed following a valid occlusion test, we became interested in such a device which has recently been released for medical monitoring. The aim of this study was to evaluate the accuracy and feasibility of using this new device in a wide range of infants, including a group of sick ventilated preterm neonates.

**MATERIALS AND METHODS**

The catheter-tip pressure transducer used in this study (MTC®, Dräger Medical Electronics, Netherlands) comprises a sensor containing a silicon pressure-sensitive chip mounted on an extremely flexible #3 French gauge plastic catheter. The pressure transducer is designed for invasive diagnostic applications requiring accurate physiological measurements. When not in use, the MTC® is kept in a protective plastic tube, which also serves as a calibration chamber. The pressure range is −40 to +40 kPa with a maximum linearity error of 0.5%. The frequency response stated by the manufacturer (3 dB = 100 kHz) should be more than adequate for infant lung function tests, even in rapidly breathing preterm neonates. The output of the MTC® (±2 mV) was amplified using an amplifier built by our engineering departments to bring the signal size into the range of ±5 V. The signal was digitized using an Analog Devices RTI 815 converter card, and data was collected using an IBM-compatible personal computer with either RASP software (Respiratory Analysis Program, Physio Logic, Newbury, England), or a data acquisition program designed by the computer engineering department in Hannover (D. Heinrich).

**Calibration of the MTC®**

The MTC® was prewetted for at least 1 hour before use by submerging it in sterile water, as recommended by the manufacturer to reduce drift during calibration and measurement. The MTC® was then placed in its calibration chamber at atmospheric pressure and the output of the amplifier was zeroed. The calibration chamber was then attached to a water-filled manometer and +1.964 kPa (20 cmH₂O) pressure was applied to allow calibration. During the in vivo assessments, calibration and zero offset were checked after each study by applying 0 and +1.964 kPa (20 cmH₂O) signals, using the water-filled manometer.

**In Vitro Assessments**

As the MTC® was being used with an amplifier, an in vitro assessment of linearity and frequency response of the transducer with amplifier was performed. The linearity of the MTC® was assessed across the range −2.946 to +2.946 kPa (−30 to +30 cmH₂O). The MTC® and a Validyne MP45 ± 5 kPa differential pressure transducer were calibrated using simultaneously applied 0 and +1.964 kPa (20 cmH₂O) pressure signals with a water manometer. A series of pressures in approximately 0.5-kPa increments from −2.946 to +2.946 kPa were then applied, the exact applied pressure being measured using the Validyne MP45. The frequency response of the MTC®, when used in conjunction with the specially designed amplifier, was assessed using the pressure chamber method described by Vallinis and coworkers.21,22 The pres-
TABLE 1—Characteristics of the Infants Studied

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spontaneously breathing</th>
<th>Ventilated</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>angenital age (weeks)</td>
<td>27.5 2 3 ^ 0</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>1.89</td>
<td>1.05</td>
</tr>
<tr>
<td>Age (weeks)</td>
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<td>Length (cm)</td>
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</tr>
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<td>36.5</td>
</tr>
<tr>
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<td>25-41</td>
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<tr>
<td>Median Range</td>
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</tr>
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</table>

sure chamber method was also used to assess the phase relationship of the MTC® and a Hans Rudolph 0-10 L min⁻¹ PNT, alone and when attached to a 2.5-mm I.D. endotracheal tube, with a Furness ± 0.2-kPa differential pressure transducer as used for the in vivo measurements.

In Vivo Assessments

Subjects

The in vivo assessment involved the measurement of lung mechanics in neonates and infants. We studied 51 spontaneously breathing infants and small children aged 1 day to 24 months—including 9 healthy neonates, 42 infants with cardiopulmonary disease—and 18 ventilated infants between 1 day and 3 months old. In the spontaneously breathing infants, the weight ranged from 1.35 to 12.0 kg (median 2.6 kg), the median weight in the ventilated infants was 1.145 kg (range: 0.60 to 4.0 kg). Infant details are presented in Table 1. With the exception of the healthy neonates, the infants had a variety of cardiopulmonary illnesses, including neonatal respiratory distress syndrome, chronic lung disease of prematurity, and interstitial lung disease. The ventilated infants were nasotracheally intubated and were receiving synchronized intermittent mandatory ventilation on either a Hoyer Infant Star ventilator or a Dräger Babylog 8000. Only infants who were breathing spontaneously between mandatory breaths and were stable during a short period of continuous positive airway pressure ventilation were studied. All infants were continuously monitored with a pulse oximeter. In addition, the ventilated infants usually had monitoring of transcutaneous PO₂ and PCO₂.

Measurement Methods

Pao was measured from a port inside the PNT (Hans-Rudolph 0-10 L min⁻¹) when studying ventilated preterm neonates and small infants, and from a port between face-mask and the PNT in the older spontaneously breathing infants. The pressure port was attached to a pressure transducer (Furness ±5 kPa in London, UK Sensor Technics 144SC in Hannover, Germany). Ptp was obtained by subtracting Pes from Pao.

Flow was measured using a heated Hans-Rudolph PNT (0-10 L min⁻¹ or 0-30 L min⁻¹) according to the size of the infant studied connected to a pressure transducer (Furness 0.2 kPa, SensorTechnics). A Rendell-Baker face mask size 0 or 1 was used for nonventilated infants, and in ventilated infants, the PNT was attached between the endotracheal tube connector and ventilator circuit. The flow signal was digitally integrated to obtain volume. The transducers were calibrated using known signals before each study and checked afterward.

All analog signals were sampled at 100 Hz and digitized, using an Analog Devices A-D converter, then displayed and recorded on personal computers, using RASP software in London or a data acquisition program designed by the computer engineering department (D. Heinrich) in Hannover.

Procedure

The catheter was sterilized in activated glutaraldehyde solution and rinsed thoroughly. After prewetting for at least 30 minutes and calibration, the catheter was passed through the nose into the stomach, as shown by positive pressure swings during inspiration. The MTC® was then withdrawn through the cardiac sphincter into the lower third of the esophagus, as shown by downward deflection of the pressure signal during inspiration. The MTC® position was then adjusted if necessary to achieve maximal swing with minimal cardiac artifact. Passing the catheter orally, as originally intended, proved difficult because its extreme flexibility often resulted in the catheter coiling in the back of the throat. With the MTC® in position, the face mask and PNT were placed over the infant’s mouth and nose, using silicone putty to obtain an airtight seal in the spontaneously breathing infants. In ventilated infants, the PNT, with a silicone valve for subsequent airway occlusions, was attached between the tube connector and ventilator circuit. In the presence of a leak around the endotracheal tube, gentle pressure was applied to the larynx. All measurements on infants with cardiorespiratory disease were conducted as part of a clinical assessment at the request of the attending physician; healthy infants were recruited from the maternity wards and the special care baby unit. Written informed consent was obtained from the parents of the healthy infants. Verbal consent to use the new device was obtained from all other...
parents, since the measurements were part of a routine lung function assessment requested by the attending clinician. Parents were frequently present during the measurements. The study had approval from the local ethical committee at both centers.

The measurements were performed during natural sleep in all healthy neonates and in the ventilated infants. The other infants, who were studied as part of their clinical lung function assessment, which included whole body plethysmography, were sedated with choral hydrate 60–80 mg kg⁻¹. Analysis was restricted to periods of quiet sleep as assessed by behavioral criteria. With the head in a neutral position (e.g., not rotated, slightly extended), occlusions were performed manually at end-inspiration for two to three respiratory efforts. This procedure was repeated at least three times if the infant remained asleep. To minimize disturbance to the ventilated infants, data collection for dynamic mechanics commenced as soon as a satisfactory occlusion test had been obtained. In the ventilated infants, two different approaches were used to perform the occlusion test. In those infants in whom a silicone valve was used, the occlusion was performed by clamping the silicone valve at end-inspiration. Following a successful occlusion test, the valve was removed to reduce the dead space. In very small infants, when it was felt that the dead space, including the valve (3.2 ml) would be excessive, the valve was omitted and the PNT briefly disconnected to perform the occlusion manually.

Data Analysis

Occlusion tests were analyzed by hand, calculating the mean ratio of peak-to-peak ΔPes/ΔPao for each occlusion and expressing results from each infant as the mean of two to three occlusions. Dynamic mechanics were calculated using multiple linear regression analysis (Anadat® software, Montreal, Canada). At least 10 regular consecutive breaths from a period of quiet sleep were analyzed to obtain Cdyn and Rdyn. However, in three of the ventilated infants, only eight or nine consecutive regular breaths could be recorded, and these were used for calculation of dynamic mechanics. Only results with a coefficient of determination (r²) of 0.95 are reported.

RESULTS

In Vitro Studies

The linearity check gave satisfactory readings within 2% between ±2.946 kPa (±30 cmH₂O) (Fig. 1). Assessment of the frequency response of the MTC® in conjunction with the amplifier showed a satisfactory frequency response to at least 10 Hz. At 10 Hz the attenuation was 0.94 (Fig. 2) and there was no measurable phase lag. Assessment of the phase relationship of the MTC® and the Hans-Rudolph PNT with a Furness pressure transducer showed that the PNT signal lagged slightly behind the MTC® signal when signals between 1 and 5 Hz were applied (Fig. 3). The addition of an endotracheal tube produced no significant further phase lag.

In Vivo Studies

The catheter was easy to pass in all infants including the smallest preterm neonates and those in natural sleep. Following positioning it was well tolerated and relatively few episodes of esophageal spasm were observed, even after repositioning. Minimal repositioning was necessary to obtain satisfactory occlusion tests in all infants studied. The calibration checks performed after each study showed a mean (SD) change in the zero (baseline) pressure of -0.017 (0.239) kPa [p = 0.8, 95% confidence interval (CI) of the difference -0.159; 0.150] over a median (range) time of 170 (62–407) minutes. The applied pressure change of 1.964 kPa (20 cmH₂O) was measured as a mean (SD) of 1.966 (0.05) kPa (range: 1.87–2.03 kPa), with no significant difference between the pre- and post-measurement checks (p = 0.96).

For the spontaneously breathing, nonventilated infants, the ratio of esophageal to airway opening pressure changes (ΔPes/ΔPao) ranged from 0.94 to 1.09, mean (SD) 1.013 (0.03). ΔPes/ΔPao was just outside the ±5% range in 7 of the 51 nonventilated infants, one of whom was a healthy preterm infant. In the absence of a leak around the endotracheal tube, ΔPes/ΔPao ranged from 0.98 to 1.06, mean (SD) 1.003 (0.02) in the ventilated infants.
Infants with only one infant having a $\Delta$Pes/$\Delta$Pao ratio greater than 1.05. The ratio of $\Delta$Pes/$\Delta$Pao during an airway occlusion was not statistically different between the groups ($p = 0.18$; 95% CI: -0.023; 0.0004). $\Delta$Pes vs $\Delta$Pao during an airway occlusion are shown for each subject of the three groups (ventilated, healthy, and sick nonintubated infants) separately in Figure 4.

Calculated values of $C_{dy}$ and $R_{dy}$ for each infant are plotted against weight in Figures 5 and 6, respectively. Despite a valid occlusion test, we failed to get an $r^2 \geq 0.95$ in 6 of the 51 (12%) nonventilated and 1 of the 18 (6%) ventilated infants, using multiple linear regression for the desired range of 10 Hz being 0.94. There was no measurable phase lag between the applied and measured signal up to 10 Hz.

**DISCUSSION**

The MTC® has a stable, linear calibration and physical characteristics suitable for use in rapidly breathing infants. The in vivo calibration checks after each study showed that a pressure change of 1.964 kPa (20 cmH$_2$O) was measured to within 5% in every infant after ≤407 minutes. The zero instability found in the in vivo studies was within that claimed by the manufacturers (≤0.5 kPa over 16 hours at 37°C). Fortunately dynamic mechanics measurements do not require absolute measurement of Pes. A potential problem with the MTC® is the very low voltage output, such that an amplifier is needed in order to use the catheter with a ±5 to 10V A-D converter. Despite the addition of a powerful amplifier, the frequency response of the MTC® remained satisfactory to at least 10 Hz, which should be adequate for dynamic mechanics measurements. Assessment of the phase relationship of the MTC® and a Hans-Rudolph PNT with a Furness pressure transducer showed the PNT lagged slightly behind. This can be explained by the need for fine bore tubing between the PNT and transducer, and will obviously vary according to the precise characteristics of the flow measuring device and circuitry employed. When using esophageal balloons or fluid-filled catheter manometry, the presence of catheter tubing between the site of pressure measurements and the transducer is likely to introduce an equivalent delay to that occurring for the flow signal, while transmission from the MTC® will be more instantaneous. When calculating compliance, errors of less than 8% occur, even when the phase mismatch is approximately 20 degrees. However, more significant errors occur when measuring resistance, and it has been suggested that delays in pressure and flow measurement systems should match within 1 ms (i.e., 4-degree phase lag at 10 Hz). Introduction of a 1-ms delay in the MTC® signal would have reduced the phase lag between flow and pressure to 4-degrees at 5 Hz with the circuitry used in this study. Having now demonstrated that the MTC® is a suitable device for esophageal manometry in infants,
We were able to demonstrate that it is possible to achieve accurate occlusion tests in a wide range of infants, including tiny premature neonates receiving respiratory support for respiratory failure. The microtransducer catheter avoids several problems that may potentially limit the usefulness of alternative techniques for esophageal manometry in infants. The 3-FG catheter on which the microtransducer is mounted is far smaller than the catheter diameter conventionally recommended for either mounting an esophageal balloon or for fluid-filled catheter manometry because the frequency response of the transducer is not influenced by length and diameter of the catheter. Thus, it is more appropriate in size and less disturbing for very small infants. Although this technique remains minimally invasive as it requires placement of the catheter in the esophagus, the 3-FG MTC® caused minimal disturbance even in tiny premature infants so that repeated measurements to evaluate therapeutic interventions are feasible. However, whichever technique is used, esophageal manometry can only be validated in infants stable enough to make respiratory efforts during airway occlusion, and in whom leaks around the endotracheal tube can be abolished.

Although there was variability between individual subjects, the ΔPes/ΔPao ratio during airway occlusion was between 0.95 and 1.05 in all but 8 of the 69 infants studied. Reasons for obtaining a ratio both greater or less than unity have been discussed in detail previously and include air leaks we took care to exclude, and upper airway obstruction with failure to achieve pressure equilibrium at the airway opening. Loss of hypopharyngeal muscle tone may be a problem, especially in sick infants, in whom large negative intraesophageal pressure swings will be exerted during airway occlusion. In one of the nonventilated infants in this study, narrowing of the upper airways led to a ΔPes/ΔPao ratio that was initially greater than unity during airway occlusion. This was, however, corrected by increasing neck extension and reducing air-

![Graphs of occlusion test at end-inspiration. ΔPao is plotted against ΔPes for each individual infant with the line of identity shown. (A) Ventilated infants (n = 18). y = 0.99x + 21.77 (r² = 0.999). (B) Spontaneously breathing healthy infants (n = 9). y = 1.02x - 7.99 (r² = 0.997). (C) Spontaneously breathing infants with cardiopulmonary diseases (n = 42). y = 1.01x + 0.42 (r² = 0.985).](image)
signal distortion due to cardiac artifacts. However, compared to our own experiences when using an esophageal balloon and a fluid-filled catheter, the failure rate with the MTC® was low, and the reported problems were not particularly prominent in the very small, sick infants.

The calculated mechanics in our series of sick and healthy infants are in accordance with published data. Cdyn values in healthy infants have ranged from 11 to 20 ml kPa⁻¹ kg⁻¹, whereas Rdyn may range from 1.0 to 10.0 kPa.L⁻¹ s⁻¹ in small preterm infants. As expected, the values calculated from infants with cardiopulmonary disease tended to be lower for Cdyn and higher for Rdyn than values obtained in healthy infants. Our values in ventilated preterm infants are also comparable to those reported previously. It is possible that micromanometry may also be suitable for use in fully ventilated subjects if a satisfactory method of validating Pes as a reflection of Ppl under these conditions is developed. One such method involving abdominal compression during airway occlusion has been described recently.

In conclusion, this new microtransducer catheter appears to be a valuable tool for measuring pleural pressure in a wide range of infants, including very small, ventilated, sick preterm infants. A satisfactory occlusion test could be obtained in all infants to demonstrate its validity. By avoiding problems of the more established esophageal balloon or fluid-filled catheter manometry, such as frequent flushing, inappropriate balloon size, or esophageal spasms, it may prove to be a better method of measuring dynamic pulmonary mechanics in all groups of infants.

One potential problem with the MTC® is that, since it does not require transmission of pressure along tubing to a transducer, phase differences can arise when making simultaneous flow measurements with a PNT. This phase lag should be allowed for in either amplifier or, preferably, software design. Finally, since problems resulting from inhomogeneous distribution of pleural pressure or failure to equilibrate during occlusion may still occur, irrespective of the technique used, careful validation and interpretation of all measurements will remain mandatory.

ACKNOWLEDGMENTS

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To the Editor: Comparison of Dynamic and Passive Respiratory Mechanics in Ventilated Newborn Infants

We are concerned that the recent article by Kugelman et al. (Pediatric Pulmonology, 1995; 20:258-264) may contain several fundamental errors to the extent that the conclusions are not justified by the results presented. The authors describe a study in which two automated infant respiratory function monitors have been used to calculate total respiratory mechanics in ventilated infants, using either dynamic measurements throughout the breath or passive expiratory flow volume curves, following brief end-inspiratory occlusions. The authors conclude that both methods were easy to use and that, although there were significant differences between various approaches (which they attributed to changes in functional residual capacity [FRC] according to measurement conditions) "meaningful results could be obtained using either monitor since there was "good correlation" between the various approaches.

We would challenge these conclusions on the following grounds:

1. The Bicore CP 100 monitor is not "easy to use" in the normal clinical setting unless all respiratory efforts are suppressed as in the current study. Adjustment of ventilator settings to achieve this state may have significant effects on the measured values. Furthermore, data collection has to be interrupted for at least 30 seconds if a print-out of results is to be obtained. To perform airway occlusions every fourth breath, as described in this study, would necessitate simply jotting down the results from the screen with no time for any quality control of the reported data. Any patient effort will invalidate recorded data.

2. It is unlikely that reliable results would be obtained with the Bicore CP 100 occlusion technique during intermittent positive pressure ventilation (IPPV). When using the Bicore valve, the infant exhales directly into the ventilator circuit and not to atmosphere as stated in this manuscript. This itself violates many of the assumptions of the single breath technique. In addition, the algorithms used are unusual and inappropriate, as they do not allow for extrapolation to passive elastic equilibrium volume.¹

3. Despite reaching statistical significance, the correlation between some of the indices was in fact rather poor and biased by one or two outliers (their Fig. 4). More importantly, the finding of even a "good correlation" between two methods provides absolutely no evidence about underlying accuracy, reliability, or relevance of results. It is now generally recognized that comparison of two methods using regression analysis is a totally inappropriate statistical approach and that 95% limits of agreement, as described by Bland and Altman,²,³ should be calculated. If the results from the Kugelman et al. study were to be plotted using this approach, the true magnitude of the discrepancy between the various approaches would readily become apparent.

4. The values of expiratory resistance are lower than the expected resistance of an endotracheal tube alone in several of the infants, which suggests errors in the calculation of this parameter due to linearity of the pressure volume curve.⁴

In conclusion, we would suggest that the discrepancies between the various techniques reported in this study are far more likely to have arisen from application of inappropriate techniques or algorithms than for any of the physiological reasons proposed by the authors. In particular, explanations based on changes in FRC are unlikely to be relevant as the occlusion valve opens into the ventilator circuit, and the paired measurements using the PEDS and Bicore systems were made during IPPV with identical ventilator settings sufficient to suppress all respiratory efforts. Consequently, we feel that the data presented in this article should be interpreted with caution.

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REFERENCES


To the Editor: Comparison of Dynamic and Passive Measurements of Respiratory Mechanics in Ventilated Newborn Infants

We thank Drs. Stocks and Jackson for their interest in our paper (Pediatric Pulmonology 1995; 20:258–264). We stand behind our conclusion that passive and dynamic respiratory compliance and resistance measured in intubated infants are correlated, although the values measured by the passive technique are higher than those obtained by the dynamic technique. We also feel that both methods were relatively easy to use and well tolerated by the infants. The following is our response to the points raised by Stocks and Jackson.

1. We would agree that the Bicore CP100 monitor is not easy to use in healthy term or preterm infants; all of our patients were studied in the Newborn Intensive Care Unit while receiving assisted ventilation. In this group of patients pulmonary mechanics are easier to perform when compared with healthy newborns. Both methods were relatively easy to use, although we mentioned in our paper that "passive relaxation does not always occur in sick intubated newborns and therefore passive measurements may require a longer time compared to the dynamic method." Adjusting the ventilator settings for the short study period to suppress the infant's drive to breathe avoids the need for further sedation is an easy method to use in Newborn Intensive Care Units, and we and other investigators have used this method to get meaningful results. The concern in regard to the effect of adjusting ventilator settings on the measured values is academic, because studies were done on the same ventilator settings. In practice, we performed airway occlusions approximately every fourth breath, and only if an acceptable occlusion was obtained by the monitor and visually by the investigator was the occlusion accepted for analysis (criteria for acceptable occlusions were described in Materials and Methods). The mean of ten adequate breaths was used. The mean coefficient of variation was 9.5% for passive compliance and 14.3% for passive resistance.

2. In addition to dynamic measurements, the Bicore pulmonary monitor measures passive mechanics by using the single breath occlusion technique as recommended by the manufacturer. Jackson et al. reported on in vitro assessment of the Bicore pulmonary function equipment. In that study dynamic measurements were more intensively evaluated than static measurements; we agree that this needs further evaluation. In a clinical situation the use of the passive flow-volume technique (with any system) assumes a linear relationship over the volume range measured and the inactivity of respiratory muscles during expiration. Clearly, these assumptions are fulfilled when studying paralyzed infants. Therefore, the term passive is more appropriate than static measurements when using this technique. Kelly et al. recently reported comparable data to ours, showing significantly higher passive compliance and volume measurements compared to dynamic measurements in intubated newborns. We found that dynamic compliance was significantly lower (77%) than passive compliance in term and preterm infants receiving assisted ventilation, whereas Kelly et al. reported a lower dynamic compliance (71%) compared with passive compliance in 22 preterm infants before surfactant therapy (mean values 0.29 vs. 0.41 mL/cmH2O/kg).

3 and 4. There is no question that correlation does not necessarily imply agreement between 2 methods. We reported that passive and dynamic respiratory compliance and resistance are correlated (compliance more than resistance), although the values obtained by the passive technique were significantly higher than those obtained by the dynamic technique. Therefore, we are not suggesting that the 2 techniques can be used interchangeably or that one can replace the other, but instead we mentioned in our paper that sequential studies in individual patients should be performed by the same technique. We compared the 2 methods as previously done by other investigators, and we showed the differences between the methods in Figures 1 and 3. Importantly, in addition to the r-values, regression equation, and confidence limits (Figs. 2, 4), we reported the corresponding standard errors of the estimate (SEE). For instance, the SEE values were 0.19 and 0.26 mL/cmH2O for compliance in preterm and term infants, respectively; whereas they were 25 and 20 cmH2O/L/sec for resistance in preterm and term infants. With all this information, our biostatistician did not consider it necessary to include the bias and precision (95% limits of agreement) in our paper. We agree with Stocks and Jackson that the bias and 95% limits of agreement should be calculated when comparing pulse oximeter SaO2 with co-oximeter measurements of SaO2, especially when the SEE is not reported. The importance of residual plots and confidence bounds for regression lines has been discussed.

The advantages and disadvantages of different methods to measure pulmonary mechanics have been reported. Alinearity of the pressure-volume curves has also been reported. In addition, a recent paper demonstrated less intrasubject variability of compliance and resistance when mechanical breaths are analyzed as opposed to spontaneous...