Respiratory compliance in sedated and anaesthetised infants

A thesis submitted by
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for the Degree of Doctor of Philosophy

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University of London
1992
For my mother Mary
Abstract
The primary aims of this thesis were to investigate the effects of halothane anaesthesia on total respiratory compliance (Crs) in infants and young children, and to determine whether measurements obtained during anaesthesia were influenced by paralysis or inflation volume.

Sequential measurements of Crs in 20 infants, anaesthetised with halothane and nitrous oxide, demonstrated that no significant difference in Crs occurred following paralysis providing ventilation mimicked that observed in the same infant during spontaneous breathing, suggesting that paralysis per se had a minimal influence on the results.

However, when tidal volumes were increased approximately twofold, there was an immediate and highly significant increase in Crs, with individual changes ranging from 17% to 101% (mean 53%) greater than that observed during ventilation with smaller tidal volumes ($p < 0.0001$).

Paired measurements during spontaneous breathing in 17 infants before and after induction of anaesthesia demonstrated that, as in adults, halothane anaesthesia is associated with a highly significant reduction in Crs in infants. The mean reduction compared with pre anaesthetic values was 34.7% (range 0% to 58.3%), with a significant reduction in tidal volume also occurring (mean 42.5%, range 26.7% to 61.4%).

Results from 7 of these infants, in whom additional measurements during anaesthesia paralysis were possible, demonstrated that the reduction in Crs during anaesthesia could be reversed by paralysing and ventilating the infant with larger tidal volumes, approximating those observed during spontaneous breathing prior to induction of anaesthesia.

These results may have important implications for the interpretation of Crs measurements obtained from ventilated infants. Furthermore, they demonstrate that results from anaesthetised infants should not be used as reference values for conscious infants.

In addition to achieving the primary aims, work performed during the execution of this thesis resulted in

1. development of an improved method of measuring Crs in sedated infants with unstable end expiratory levels.
2. application of these techniques to infants with respiratory disease.
3. development of an interactive operator controlled system for computerised data collection and analysis.
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Influence of tidal volume on respiratory compliance in anesthetised infants and young children
Respiratory compliance during sedation, anesthesia and paralysis in infants and young children
Respiratory compliance in infants - a preliminary evaluation of the multiple interrupter technique
Lung involvement in Langerhans' cell histiocytosis: prevalence, clinical features and outcome.

Scale: throughout the text, where Figures display scale bars the following values apply:

Flow \( (\dot{V}) \) 100 ml.s\(^{-1}\)
Volume \( (V) \) 20 ml
Pressure \( (P) \) 1 kPa
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Abbreviations

Ccw  chest wall compliance
Cl   lung compliance
Cldyn dynamic lung compliance
CPAP continuous positive airway pressure
Crs  respiratory system compliance
CrsA Crs during anaesthesia, breathing spontaneously
CrsHV Crs during anaesthesia paralysis, high volume ventilation
CrsLV Crs during anaesthesia paralysis, low volume ventilation
CrsP Crs during anaesthesia paralysis, undefined ventilation
CrsS Crs during sedated or natural sleep
CT   computed tomographic (scans)
EEL  end expiratory level
f    (respiratory) frequency
FiO2 fractional inspired oxygen
FRC  functional residual capacity
IPPV intermittent positive pressure ventilation
MIT  multiple interruption technique
MOT  multiple occlusion technique
N2O nitrous oxide
O2   oxygen
P    pressure (generally equilibrated airway pressure)
PEEP positive end expiratory pressure
PFVT passive flow volume technique
PNT  pneumotachograph
Poes oesophageal pressure
Pt   tracheal pressure
Ptp  transpleural pressure
RASP Respiratory Analysis Program
Raw  airways resistance
Rcw  chest wall resistance
RI   lung resistance
Rldyn dynamic lung resistance
Rti  tissue resistance
Rrs  respiratory system resistance
TGV  thoracic gas volume
TLC  total lung capacity
Trs  respiratory system time constant

Scale: throughout the text, where Figures display scale bars the following values apply:

- Flow ( $\dot{V}$ ) 100 ml.s$^{-1}$
- Volume ( V ) 20 ml
- Pressure ( P ) 1 kPa
Acknowledgments

The work described in this thesis could not have been completed without the help and cooperation of a large number of colleagues and parents. The theatre and ward staff, anaesthetists and surgeons who accommodated us without complaint, frequently in very confined areas, deserve particular mention.

Special thanks are due to Dr David Hatch, whose continued involvement and enthusiasm ensured the continuity of data collection, often in the face of apparent adversity. Of the many other anaesthetists connected with the study I would particularly like to thank Dr Alan Yates, in at the beginning, Dr Saxon Ridley his successor, and Dr Charles Stack, for their interest and involvement in the research beyond their role as assisting anaesthetist during measurement sessions.

I am very grateful to the many parents who readily consented to measurements on their children, when the children themselves may not benefit directly, during what must have been an already stressful time immediately prior to surgery. Their trust in us and desire to benefit other children have, I hope, been justified.

The few infants who defeated my best efforts to lull them to sleep ensured that every sleeping infant was viewed with due respect, relief, and gratitude, of a sort known only to desperate parents and those measuring lung function in infants.

The thesis could not have reached this final stage without the immeasurable support, tolerance and assistance of many friends.

Without Helena and Christopher Wagstaff, and the seclusion of their home, the essential first complete draft might have been floundering still. I am indebted to them for their selfless acceptance of a mini invasion.

My thanks to Dr Elizabeth Jackson who undertook the thankless task of proof reading with a willingness and thoroughness second to none. Any remaining errors must surely have crept in since then, for little can have escaped her scrutiny.

Dr Patricia Sharp (nee Rabbette) was both a valued colleague and friend during the later stages of this thesis and a source of encouragement and understanding as we both came to write up our work.

Robert Cumberland, author of RASP software, spent many hours discussing computer capabilities and limitations. I am very grateful for his patience and perseverance.

The person entitled to most credit for this thesis is Dr Janet Stocks, without whose support, guidance and friendship none of this would have been possible. As a friend first and supervisor second, Janet's dedication was unfailing.
General Introduction

This thesis examines the application of a recently developed technique for measuring respiratory compliance, the multiple occlusion technique (MOT), to anaesthetised infants and young children.

Section 1.1 examines the historical background to the introduction of this technique, and the potential for its widespread application to measure compliance in both sick and healthy infants.

Our current knowledge about the influence of anaesthesia on respiratory mechanics is discussed in Section 1.2.

Section 1.3 presents an historical perspective on the measurement of respiratory mechanics in anaesthetised infants, revealing the deficit in current knowledge which this thesis sought to correct.

Subsequent Sections describe the application of the MOT to sedated, anaesthetised, and anaesthetised paralysed infants. The apparatus and technique are discussed in detail in Section 2, and the results of measurements are reported in Section 3.

Section 4 describes an adaptation of the MOT, and the results of a comparison between measurements of compliance made in the same infants using three related techniques.

A detailed discussion of the results of the previous 2 sections is given in Section 5.

Finally, the implementation of computerised data collection, handling, and analysis is described in the Appendix.
Section 1

Historical introduction

Section 1.1

The history of lung mechanics measurements in infants and young children.

Attempts to quantify the respiratory parameters of infants have been documented for over 100 years (table 1.1). Early methods such as the multiple pen displacement system of Eckerlein 1890, or spirometric volume displacement used by Dohrn 1895, were extremely cumbersome, had excessive dead space, or resulted in unacceptable levels of rebreathing and were thus unsuitable for general use.

With the introduction of an infant head-out plethysmograph by Murphy in 1931, accurate measurement of volume and frequency could be achieved with minimal influence of equipment on the measured parameters. Further refinements by Cross in 1949, who replaced the tightly stretched membrane around the face with an inflatable cuff, increased the ease of use of the plethysmograph and resulted in numerous applications to study both basal ventilation, and ventilatory responses to changes in inspired CO$_2$ and O$_2$. In 1953 Mead described the measurement of lung resistance and dynamic compliance using oesophageal balloons to measure transpulmonary pressure changes in adults. Cook (1955) and McIlroy (1955) applied this method of measuring respiratory mechanics to infants, using the plethysmograph to measure tidal volume changes.


However, these techniques are not without their limitations. Whole body
plethysmography requires highly specialised and bulky equipment, and skilled operators to achieve reproducible and accurate results. This applies especially to airways resistance measurements where inspired air is required to be of the same temperature and humidity as expired air. In addition the infant must be self ventilating and stable, unless extensive modifications are made to the equipment and experienced medical personnel are present during measurements (Hatch 1976, Helms 1982). Techniques using oesophageal balloons or catheters, for indirect measurement of pleural pressure changes, need less bulky but equally sensitive equipment, which requires considerable skill to use successfully. Interest in oesophageal manometry waned when it was found that chest wall distortion or other causes of unequal transpulmonary pressure appeared to invalidate the measurements in small infants, particularly those receiving assisted ventilation for respiratory distress syndrome of the newborn (LeSouef 1983, Thomson 1983, Heaf 1986). In addition, it was reported that the accuracy of oesophageal pressure recordings may be adversely affected in anaesthetised infants (Helms 1982).

Besides plethysmography and oesophageal manometry, other techniques were being developed and applied to study the respiratory mechanics (and lung volumes) of infants. Most such methods had similar limitations in their application, and many were least appropriate for the sick infants most in need of some form of lung function monitoring.

Volume jackets, inflated around the trunk, measured volume displacement which, when coupled with oesophageal and airway pressure measurements, could be used to measure static and dynamic compliance in anaesthetised, and chronically ventilated, infants (Milner 1972, Hatch 1981). This required the infant to be virtually immobile except for respiratory movement, and was less sensitive than pneumotachography in measuring volume changes. Super syringes were used in anaesthetised paralysed infants and children to perform stepwise inflations and deflations and thus construct volume pressure curves from the corresponding pressure to volume changes (Nightingale 1965, Lunn 1968). As with the volume jackets, airway pressure measurements allowed total compliance to be measured, oesophageal pressures lung compliance. Nightingale (1965) used stepwise increases in airway pressure and measured the corresponding increases in passively expired lung volume to construct the volume pressure curve.

Such techniques could only be utilised in infants who were either anaesthetised or very heavily sedated, to the extent that apnoea could be
induced. In addition, most proponents of super syringe techniques were measuring respiratory parameters at lung volumes outside the tidal volume range.

Motoyama (1977), studying anaesthetised children, applied negative pressure to the airways of patients after inflating the lungs to 40 cmH₂O (nominally designated total lung capacity). In this way maximal expiratory flow volume curves were obtained from children otherwise too young to perform the manoeuvre.

Adler (1978) first described a means of obtaining partial expiratory flow volume curves in normal non-anaesthetised infants by means of rapid thoraco-abdominal compression (the "squeeze" technique). This technique was further developed by Taussig (1982), Godfrey (1983) and Tepper (1986) and, due to its relative simplicity, has become one of the most extensively used techniques for assessing airway reactivity and function in infants.

Of the numerous techniques to measure respiratory mechanics which had been introduced by the end of the nineteen seventies, none had found widespread application, with plethysmography and oesophageal manometry remaining the established basis of infant lung function measurement. Many of the normal values being quoted at this time were obtained during anaesthesia, and applied only to infants measured in similar circumstances using comparable techniques.

The occlusion techniques
In 1954 Comroe first described the measurement of respiratory mechanics using a passive expiration, in his case in paralysed anaesthetised cats and human adults. The measured pressures, volumes, and flows depended on total relaxation of the respiratory system, restricting the use of this technique to the paralysed or highly trained subject (McIlroy 1963, Bergman 1969).

In 1960, Cross described the apnoea resulting from prolonged inflation in newborn infants, ascribing the response to the Hering Breuer inflation reflex (Breuer 1868, Hering 1868). The prolongation of expiratory time (an apnoeic pause) was felt to be the manifestation of inhibition of inspiratory effort, and believed to decrease rapidly in intensity in the first weeks of life. It was not until the early 70's that this apnoea was found to be associated with muscle relaxation when studied in animals (Younes 1974).

The possibility of using this induced relaxation to measure passive respiratory mechanics was first postulated by McIlroy (1963) and subsequently applied to
animals by Thach (1976) and Zin (1982). Olinsky (1974), and Thach (1978), found that they could successfully induce and study relaxed expiration by evoking the Hering Breuer inflation reflex with inspiratory airway occlusions in human infants.

Olinsky took this further and in 1976 described in greater detail a means of measuring respiratory system compliance ($C_{rs}$) in infants by using brief airway occlusions at different inspiratory lung volumes during tidal breathing. During each occlusion, with its brief respiratory pause, airway pressure equilibrates throughout the lungs (Fig 1.1). This pressure, measured at the airway opening, is proportional to the volume of air in the lungs at the time of occlusion. Thus a plot can be constructed of volume above end expiratory level at the time of occlusion against equilibrated elastic recoil pressure (or plateau pressure $\delta P$), Fig 1.2.

By fitting the best fit line to this plot, respiratory compliance is derived, being the slope of the line

$$V = Crs \times P + k,$$

($V =$ occluded volume, $P$ pressure measured at the airway opening, $k$ a constant - the intercept of the volume axis at $P = 0$).

i.e. $C_{rs} = \frac{\text{Volume}}{\text{Pressure}}$ (where $k = 0$).

Modifying the technique by using expiratory occlusions, Mortola (1982) improved both the likelihood of successfully obtaining a measurement and the reproducibility of the measurements when studying term normal infants. In this paper, Mortola also described the use of the Hering Breuer inflation reflex to obtain the expiratory time constant of the respiratory system ($T_{rs}$) as described by McIlroy (1963), and thus obtain values for total respiratory resistance ($R_{rs}$) from the relationship $T_{rs} = C_{rs} \times R_{rs}$.

LeSouef (1984a) took this one stage further. Measuring the occlusion pressure ($\delta P$), and $T_{rs}$ following release of an end inspiratory occlusion, he obtained $C_{rs}$ by extrapolating the slope ($T_{rs}$) to zero flow, assuming linear expiration to be terminated early by inspiratory effort, $C_{rs}$ being extrapolated expired volume $\div$ occlusion pressure. The presence or absence of respiratory effort during this passive flow - volume technique (PFVT) was assessed by LeSouef using magnetometers.

There was now a method of measuring respiratory mechanics in the spontaneously breathing infant which required simple compact equipment,
Figure 1.1  Brief airway occlusion during expiration (adaptation of Olinsky's inspiratory occlusions). Note equilibration of airway pressure during occlusion.

Figure 1.2  V - P data from 12 occlusions throughout expiration. Occluded volume above end expiratory level plotted against equilibrated airway pressure during the occlusion.
could be taken to the bedside, and was adaptable for similar measurements in the mechanically ventilated infant. In the presence of a truly linear expiratory flow volume slope, Rrs and Crs could be calculated using the single breath method. In the presence of alinearity due to diseased lungs or to expiratory effort following release of the occlusion, Crs could still be measured using the multiple occlusion technique, providing there was relaxation with constant pressure plateau indicating equilibration throughout the lungs during the occlusions.

During recent years these techniques have been applied to different groups of infants. The passive flow volume technique (PFVT) has been applied to neonates and infants, both self ventilating and receiving controlled ventilation (Mortola 1982, LeSouef 1984a, Thomson 1985b). The multiple occlusion technique (MOT) has been used to measure total compliance in pre-term infants (Simbruner 1982), sick intubated and very low birth weight infants (Thomson 1983) and infants up to one year of age (Thomson 1985a).

The multiple occlusion technique was technically simple in concept and application, and required no change of apparatus to measure the same infant in different ventilatory states. Success depended simply on relaxation during an occlusion, be this due to the Hering Breuer inflation reflex, lack of muscle activity because of induced paralysis, or absence of respiratory drive.

Apart from the recording and signal processing equipment, the hand held apparatus consisted of a shutter with pressure port and a pneumotachograph for measuring flow and volume. This apparatus was attached to a mask for non-intubated infants, or directly to the tracheal tube with appropriate connectors. Various modifications have been made to adapt such a system to different ventilator systems, minimise dead space, or allow manual ventilation (LeSouef 1984a, Thomson 1985b). The system remains more manageable than the whole body plethysmograph and is technically easier to use than oesophageal manometry.

The introduction of these potentially simple techniques has resulted in a significant increase in the number of studies carried out into infant lung mechanics and response to therapies, spurred on by the advances in neonatal intensive therapy and improved survival.
Historically, because of the greater ease with which anaesthetised infants could be studied, most early measurements in infants with respiratory or cardio-respiratory disease relied on data from anaesthetised paralysed infants and children for normal reference values. These latter infants were assumed to be in a completely passive state, with no respiratory effort influencing results so obtained (Nisbet 1971, Thomson 1985a).

At the time of the study described in this thesis, no single technique had been applied within the same infants to assess the influence of anaesthesia on total respiratory compliance. Similarly, no studies had compared values during anaesthesia in infants breathing spontaneously with those obtained during muscle paralysis and controlled ventilation.
Table 1.1  Summary of measurements of respiratory mechanics in infants: progressive techniques

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Method</th>
<th>Parameters measured</th>
<th>Key to abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckerlein</td>
<td>1890</td>
<td>Pen displacement</td>
<td>volume changes</td>
<td>Crs, Cl, Ccw</td>
</tr>
<tr>
<td>Dohrn</td>
<td>1895</td>
<td>Spirometer</td>
<td>volume and frequency</td>
<td></td>
</tr>
<tr>
<td>Murphy</td>
<td>1931</td>
<td>Head out plethysmograph</td>
<td>volume and frequency</td>
<td></td>
</tr>
<tr>
<td>Cross</td>
<td>1949</td>
<td>Head out plethysmograph with cuff</td>
<td>basal ventilation, O₂ and CO₂ stimulus response</td>
<td></td>
</tr>
<tr>
<td>Cook</td>
<td>1955</td>
<td>Oesophageal balloons + head out plethysmograph</td>
<td>respiratory mechanics and tidal ventilation</td>
<td></td>
</tr>
<tr>
<td>McLlroy</td>
<td>1955</td>
<td>Oesophageal balloons + head out plethysmograph</td>
<td>respiratory mechanics and tidal ventilation</td>
<td></td>
</tr>
<tr>
<td>Berglund</td>
<td>1956</td>
<td>Helium dilution</td>
<td>lung volume (FRC)</td>
<td></td>
</tr>
<tr>
<td>Cook</td>
<td>1958</td>
<td>Helium dilution</td>
<td>lung volume (FRC)</td>
<td></td>
</tr>
<tr>
<td>Auld</td>
<td>1960</td>
<td>Plethysmograph</td>
<td>thoracic gas volume (TGV)</td>
<td></td>
</tr>
<tr>
<td>Polgar</td>
<td>1961</td>
<td>Plethysmograph</td>
<td>thoracic gas volume, airways resistance</td>
<td></td>
</tr>
<tr>
<td>Lunn</td>
<td>1968</td>
<td>Super syringe (anaesthetised patients)</td>
<td>Crs, Cl, Ccw</td>
<td></td>
</tr>
<tr>
<td>Doershuk</td>
<td>1969</td>
<td>Plethysmograph</td>
<td>thoracic gas volume, airways resistance</td>
<td></td>
</tr>
<tr>
<td>Wohl</td>
<td>1969</td>
<td>Forced oscillations (extra-thoracic)</td>
<td>respiratory resistance (from impedance)</td>
<td></td>
</tr>
<tr>
<td>Milner</td>
<td>1970</td>
<td>Pressure jacket</td>
<td>tidal ventilation</td>
<td></td>
</tr>
<tr>
<td>Milner</td>
<td>1972</td>
<td>Pressure jacket and oesophageal balloon</td>
<td>Crs, Cl</td>
<td></td>
</tr>
<tr>
<td>Cogswell</td>
<td>1973</td>
<td>Forced oscillations (airway)</td>
<td>respiratory resistance</td>
<td></td>
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<tr>
<td>Oflinsky</td>
<td>1976</td>
<td>Airway occlusion, tidal breathing</td>
<td>Crs</td>
<td></td>
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<tr>
<td>Stocks</td>
<td>1977</td>
<td>Modified plethysmograph and resistance circuit</td>
<td>thoracic gas volume, airways resistance</td>
<td></td>
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<tr>
<td>Motoyama</td>
<td>1977</td>
<td>Negative airway pressure forced expiration (intubated, anaesthetised or sedated)</td>
<td>maximal expiratory flow volume curves</td>
<td></td>
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<tr>
<td>Adler</td>
<td>1978</td>
<td>Positive thoracic pressure forced expiration (sedated)</td>
<td>partial forced expiratory flow volume curves</td>
<td></td>
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<tr>
<td>Taussig</td>
<td>1982</td>
<td>Thoraco-abdominal compression (PEFV)</td>
<td>partial forced expiratory flow volume curves</td>
<td></td>
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<tr>
<td>Mortola</td>
<td>1982</td>
<td>Modified occlusion technique + passive expiration</td>
<td>Crs and Trs</td>
<td></td>
</tr>
<tr>
<td>LeSouëf</td>
<td>1984</td>
<td>Single breath passive flow volume technique</td>
<td>Crs, Rrs, Trs</td>
<td></td>
</tr>
</tbody>
</table>
Section 1.2

Anaesthesia and respiratory mechanics

From the very early days of inhalation anaesthesia, in the mid 19th Century, altered patterns of respiration in adults anaesthetised with the new inhaled anaesthetics, ether and chloroform, had been reported (Snow 1858). With the passage of time and with the aid of improved technology, a more detailed picture has been constructed of the changes which occur as a result of anaesthesia. The data upon which current theory is based have been obtained almost exclusively from adults and from animal models.

Functional residual capacity (FRC)

Induction of anaesthesia in supine adults was found to result in a cephalad movement of the diaphragm at functional residual capacity (FRC) (Froese 1974), which was itself shown by early workers to be reduced following induction of anaesthesia (Westbrook 1973, Hewlett 1974). Whether this was due to a loss of diaphragmatic tone, increased abdominal volume or other mechanisms (such as shifts in blood volume, or changes in chest wall compliance) was at that time unclear (Jones 1979).

The reduction in FRC occurring on induction of anaesthesia was not altered further by neuromuscular paralysis (Westbrook 1973). Hickey (1973) found a similar reduction in FRC occurred whether the patients were self ventilating via a face mask or following suxamethonium aided tracheal intubation. The brief period of paralysis appeared to play little role in the 20% reduction in FRC.

Chest wall compliance (Cw)

The loss of muscle tone of the chest wall due to inhalation anaesthesia leads to an increased deformability of the chest wall (Vellody 1978). Since passive end expiratory lung volume is determined by the outward recoil of the chest wall being equally opposed by the inward recoil of the lungs, a change in either of these may result in a reduction in FRC. Westbrook (1973) and Rehder (1974) both reported a reduction in the outward recoil of the chest wall, probably due to a drug induced decrease in chest wall tone (Rich 1979).

Lung compliance (Cl)

The increase in lung elastance (decrease in compliance) described in earlier
studies by Rehder (1974) was thought initially to be due to the reduction in FRC and not to be its cause. The reduction in FRC and compliance were significantly less noticeable in adults anaesthetised in the seated position when compared with those measured and anaesthetised in the supine position, suggesting that any pharmacological cause was playing only a small part in events. Sedation (rather than anaesthesia) with halothane or enflurane decreases lung compliance slightly without a concomitant reduction in FRC (Gelb 1983).

Further support for the hypothesis that reduced chest wall tone was the major effector of the reduction in lung compliance came from the work of Caro (1960) and Scheidt (1981) who found that strapping the chest wall (i.e. physically increasing chest wall elastance) reduced lung compliance. However, the fact that induction of anaesthesia in adults is associated with a flattening of the slope of the pressure volume curve of the lung, as well as a shift to the right, indicates a reduction in lung compliance independent of change in lung volume (Westbrook 1973).

Pharmacological effects of the inhaled anaesthetics on lung surface tension and smooth muscle may contribute to these changes. This is supported by Gelb's finding that even sedation with halothane reduced lung compliance, and Otis' suggestion that any modulation of mechanical response by smooth muscles within the lungs could also have been affected by anaesthesia (Gelb 1983, Otis 1983). The role of surfactant at the lower tidal and absolute lung volumes seen during anaesthesia, had not at that time been explored although suggested as a possible influence on the fall in lung compliance (Marsh 1984). Subsequent studies have demonstrated disturbances both in secretion and distribution of surfactant during artificial ventilation and anaesthesia in animals and humans (Rehder 1986, Bachofen 1987).

Several investigators have commented on the measured values for lung compliance being influenced by large inflations in anaesthetised subjects (Egbert 1963, Mead 1959). Douglas (1969) found imposing periodic sighing to be effective in minimising reduction of lung compliance during anaesthesia. There were no reports of the influence of tidal volumes administered on the values obtained for compliance in comparative studies between awake and anaesthetised states.

Failure to take account of the effect of tidal volume on compliance may
have contributed to the disparity between results from early studies. Where there was some attempt to control inspired volume (Behrakis 1983), little difference was found between anaesthetised and paralysed states. Although studies controlling frequency of ventilation had been reported, (Behrakis 1983), few had been performed which investigated the effect of tidal volume alone. Visick (1973) found tidal volumes of 15 ml.kg^-1 resulted in higher values for lung compliance than did either tidal volumes of 5 ml.kg^-1 or 5 ml.kg^-1 combined with continuous positive pressure. Similarly, Grimby (1975) found tidal volumes had a direct effect on total compliance (and its component parts) during mechanical ventilation in 6 anaesthetised paralysed adults. In the adult patient requiring mechanical ventilation, Suter (1978) showed a tidal volume dependence of static respiratory compliance. This phenomenon had not been investigated in children.

**Shifts in blood volume.**
The shift of blood volume between abdomen and thorax has been suggested as contributing to the reduction in FRC, but the data available on the relative contributions of absolute volume and blood volume changes have been contradictory (Rehder 1985, Hedenstierna 1985b). Recent work suggests that there is a significant central shift of blood volume during anaesthesia (Krayer 1987).

With the introduction of computed tomographic (CT) scans, the reduction in FRC was shown to occur concomitantly with the development of unexplained densities in the dependent part of the lung (Brismar 1985) which could be reduced or eliminated with the addition of positive end expiratory pressure.

**The diaphragm**
Controversy exists over the magnitude of diaphragmatic movement following induction of anaesthesia. Hedenstierna (1985b) using CT scans found a significant cephalad displacement of the diaphragm, whilst more recently Krayer (1989), using 3 dimensional dynamic spatial reconstruction in supine adults, found little change in diaphragmatic position. Thus, whatever the initial cause of the reduction in FRC, be it loss of tone of the chest wall, changes within the lung itself, thoraco-abdominal volume shifts, or changes in diaphragmatic function, respiratory mechanics in adults are affected by anaesthesia whether as a result of the fall in FRC or other mechanical/ pharmacological changes.
Resistance

Although changes in respiratory resistance due to anaesthesia are not examined in detail in this thesis, no discussion of respiratory mechanics would be complete without some mention of the factors involved.

Resistance to gas flow in the respiratory system (Rrs) has both pulmonary (Rl) and chest wall (Rcw) components. Rl may be subdivided further into airways resistance (Raw) and pulmonary tissue resistance (Rti). The reduction in lung volume which occurs during anaesthesia leads to a secondary increase in resistance, which may also be altered by changes in tone of airway smooth muscle, oedema, the accumulation of secretions and the presence of the tracheal tube (Rehder 1986).
The effect of anaesthesia on respiratory mechanics in infants and children

Compliance
Within the normal breathing range, the slope of the pressure-volume curve of the chest wall is steeper in young than adult subjects, i.e. chest wall compliance (Ccw) is greater (Avery 1961, Muller 1979). In the infant, therefore, total respiratory compliance (Crs) reflects primarily the lung compliance (Cl). This offers the possibility of estimating Cl from Crs, which is considerably easier to measure. The lessened recoil pressure of the chest wall in young subjects results in a less sub-atmospheric pleural pressure and renders the lungs more prone to the development of atelectasis and collapse (Avery 1961).

Although the infant may be less vulnerable than the adult to a change in Crs as a direct result of a change in Ccw, any reduction in chest wall tone which permits lung volume to fall may reduce Crs indirectly. Because of the difficulties involved in measuring non anaesthetised infants, any changes in Crs due to the induction of anaesthesia in this group had not been examined.

Resistance
There are few data on the effects of inhalation or intravenous anaesthesia on pressure-flow relationships in infants and young children. The classical techniques of oesophageal manometry to measure lung resistance and whole body plethysmography to measure airways resistance are technically difficult to apply to anaesthetised infants (Section 1.1). Although it is now possible to estimate resistance of the respiratory system from a knowledge of the compliance and time constant obtained during passive flow volume measurements (PFVT, Section 1.1), Shulman (1989) has demonstrated certain problems invalidating the technique in some anaesthetised children.

No attempt was made to measure resistance in the anaesthetised infants as part of this thesis.
Section 1.3

Measurement of respiratory mechanics in anaesthetised infants and young children.

As early as 1847, Snow had reported differences in response to ether between children and adults, indicating the need to treat the younger patient as different from, rather than a smaller version of, his adult counterpart.

In the past the anaesthetised infant and child has received far more attention with respect to passive respiratory mechanics than the more difficult non-anaesthetised subject. This is due to a combination of factors, not least of which is the unconscious immobile state of the patient. The advantages of making measurements under anaesthesia include the ability to induce complete relaxation by neuromuscular paralysis, prevent air leaks by tracheal intubation (and throat packing if necessary), and the ability to control inspiratory volumes and pressures. Known volumes of gas can be introduced or removed from the ventilatory or respiratory system, and consequent airway pressure changes measured, or conversely the volume increase or decrease resulting from a known pressure change can be used to give a direct measure of total respiratory compliance. With a closed system, a complete pressure-volume curve for the lung can be constructed by controlled inflation or deflation.

Introduction of an oesophageal balloon into the system, to measure changes in transpulmonary pressure allows the partitioning of total compliance into lung and chest wall components.

Many of the early recorded studies which measured static compliance used methodology which was not readily applicable to the non-paralysed infant. Table 1.2 lists, in chronological order, published reports of techniques applied to measure lung function in anaesthetised infants. Richards (1961) inflated infants to a preset volume, relating the final equilibrated airway pressure during inflation to the subsequent passively expired volume. He noted that Crs increased when a large inflation was given just prior to the measured breath.

Nightingale (1965) used inflation to preset airway pressures of 6.8 to 34 cmH$_2$O to measure Crs, dividing the maintained pressure (held for 10 seconds) into the subsequent passively expired volume. Reynolds (1966) and Lunn (1968), also used controlled inflation techniques,
Reynolds finding little difference between static and dynamic compliance, Lunn achieving values of compliance which were lower than those predicted for awake children. Neither of these last two authors used either a volume history to ensure full lung inflation prior to measurement, or maintained the inspiratory volume or pressure for as long as Richards or Nightingale. This may have contributed to the lower values for compliance found in the later studies.

Sharp (1970), and Fisk (1970), also studied paralysed anaesthetised children by lung inflation techniques, Sharp noting the large range of values obtained from his sample whose ages ranged from 1 to 18 years. Fisk, studying the effects of thoracic surgery on lung compliance (Cl), with the chest open, noted the stabilising effect on Cl of administering a volume history prior to measurement. When measurements in air were repeated in some infants using anaesthetic gases, lower values of compliance were obtained, although technical difficulties may have accounted for this difference.

From 1970 other parameters began to be measured in the anaesthetised child, using techniques other than passive inflation or deflation. Dobbinson (1973) measured lung volume by gas dilution, and lung compliance in children aged 6 to 18 years. He found Cl to be unchanged throughout the operative period during which tidal volume had been maintained at a constant level. Dobbinson's study is also the only report of measurements of functional residual capacity (FRC) both before and after induction of inhalation anaesthesia in children. His study demonstrated a reduction of up to 35% in FRC following induction of anaesthesia and muscle paralysis, compared to pre induction values, with the greatest decreases being seen in the youngest children. Children with cardiac abnormalities were found to have less of a reduction in FRC, and lower compliance, than non-cardiac patients.

Milner (1972) measured children's ventilation using a respiratory jacket, dividing airway pressure during a period of apnoea (sustained inflation), into the volume change measured from the change in pressure within the jacket, to calculate Crs. In a later study, Hatch (1976) noted an increase in end expiratory level (EEL) as the anaesthetised spontaneously breathing child became apnoeic following administration of a muscle relaxant, and also found widely varying values for Crs, from 3 - 32 ml.cmH2O⁻¹ (= 30 - 320 ml.kPa⁻¹), in his group of patients, aged 4 months to 10 years. The increase in EEL described by Hatch was contrary to the findings in earlier studies (Dobbinson 1973, Westbrook 1973), and has not been substantiated subsequently.
By the mid 80's the volatile anaesthetic gas halothane was being examined,
particularly in relation to its influence on respiratory variables.
Murat (1985) demonstrated a dose dependent decrease in tidal volume and
increase in respiratory frequency as inspired halothane was increased from
0.5% to 1.5%. Similar decreases in tidal volume were reported later for
enflurane and isoflurane, with enflurane reducing and isoflurane not altering
respiratory frequency (Murat 1987).

Many of these early studies were performed on infants and children with
few studies performed on children of normal cardio-respiratory status were
referred to extensively as reference values for other groups, including studies
of respiratory mechanics in non-anaesthetised subjects.

Besides the changes in respiratory rate and tidal volume associated with
halothane anaesthesia, there was increasing evidence of a reduction in lung
volume (FRC), demonstrated and quantified both in adults (Westbrook 1973,
Hewlett 1974) and in children (Dobbinson 1973). This reduction in volume
was shown to be due in large part to the development of what appeared to
be atelectic areas in the dependent regions of the lungs (Brismar 1985,
Damgaard-Pedersen 1980) and visualised in CT scans of adults and children.

As discussed earlier, studies in adults had demonstrated a fall in compliance
on induction of anaesthesia, which remained unchanged following paralysis.
However, individual results of measurements following paralysis in the small
sample size of these studies show considerable variability; in some individuals
a marked increase in compliance occurred, whereas in others there was a
decrease, so that the group data showed no significant change (Behrakis
1983). No similar studies had examined the effect of anaesthesia and further
effects of paralysis on Crs in children.

The marked variability in results obtained for Crs in any sample of children
is frequently a reflection of the wide age range of those studied. The first
few years of life see a dramatic change in the components of total
compliance as the chest wall stiffens and the lung tissue becomes more
compliant with increasing age. These changes make it totally inappropriate
to extrapolate results from studies in adults to the infant and young child.

At the time of this study, no comparison had been made between the values
for Crs obtained in the anaesthetised infant and those obtained in the non -
aanaesthetised sleeping child. This reflects the many problems of measuring
the non-anaesthetised infant and the limitations of the techniques then available.

Besides the changes in respiratory mechanics which appeared to occur following induction of anaesthesia, the accompanying changes in respiratory pattern had also given rise to concern. Not only did small patients have to accommodate the changes brought about by the anaesthetic drugs, they also had to adjust to the added resistance to breathing and increased deadspace from the administering apparatus. This was causing such distress to infants undergoing repair of cleft lip and palate, breathing through a Magill system, that Ayre in 1937 designed a T-piece system without a reservoir bag or respiratory valve, with immediate improvement. With the resistance minimised, respiratory rate fell from 80 to 40 breaths per minute and the infant's general state improved.

Although authors such as Reynolds (1966) had partitioned respiratory mechanics such that he could calculate the work required to inflate an apnoeic anaesthetised infant (the work of ventilation), there were no reports until recently of the equivalent, work of breathing, being studied in spontaneously breathing infants. Later work by co-workers Hulse, Lindahl, and Hatch, and others, has explored the area of ventilation and gas exchange more thoroughly (Hulse 1984, Lindahl 1984, 1985). Besides the need for adequate fresh gas flow, it was noted that in young infants, who had not received opiate premedication, CO$_2$ clearance was significantly less efficient than in older children. These authors suggested that the high minute ventilation, representing a rapid respiratory rate rather than large tidal volume, was not compensating for the added dead space and argued that intermittent positive pressure ventilation (IPPV) may be the ventilation of choice in young infants when anaesthetised.

There are several additional reasons, besides the increase in dead space, why IPPV should be considered in younger infants, such as the greater risk of fatigue due to the increased work of breathing resulting from altered respiratory pattern during anaesthesia.

Infants normally breathe at a lung volume closer to residual volume (RV) than do adults. Although specific lung compliance is similar in infants and adults, specific compliance of the chest wall is very much higher. Thus, with the probable loss of tone and hence reduced assistance to inspiration, which occurs as a result of anaesthesia (Rehder 1986), and the lower lung volume requiring greater pressures for inflation, the infant's respiration may be compromised considerably. Besides this, the infant's more horizontal
configuration of the rib cage compared with the adult's bucket-handle configuration acts to limit the potential for thoracic expansion. (Openshaw 1984). The rib cage - diaphragm - abdominal and accessory muscle respiratory pump is thought to be less efficient in young children because of chest wall instability. Tusiewicz (1977) observed that rib cage contribution to ventilation is depressed during halothane anaesthesia in children. Keens (1978) found that the infant has fewer type 1 oxidative muscle fibres in the diaphragm, and is therefore potentially more prone to fatigue than an adult. These observations suggest that not only would ventilatory efficiency be poorer still, but that the infant's reserves may be much more limited than when not anaesthetised.

In view of the finding that Crs is reduced in adults following induction of halothane anaesthesia, it became clear that it was probably inappropriate to use values for compliance obtained from anaesthetised children as reference values for non-anaesthetised infants. Also, since it was possible that total compliance might be altered by paralysis, it would seem appropriate to clarify any such effects before relying on Crs values so obtained as representative of any state other than anaesthesia paralysis. Given the differences discussed above, between infants and adults, greater knowledge was needed of the effect of anaesthesia on respiratory compliance in infants.
<table>
<thead>
<tr>
<th>Author and Date</th>
<th>Technique and Parameters</th>
<th>Subject group</th>
<th>Ventilation</th>
<th>Results, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snow 1847</td>
<td>Observation</td>
<td>All ages</td>
<td>Self ventilation in ether + air</td>
<td>Children anaesthetised in 2-3 minutes adults 3-6</td>
</tr>
<tr>
<td>Richards 1961</td>
<td>Paralysed. Inflated to set P (5-25 mmHg) for 10 s, passive deflation via spirometer</td>
<td>n=21 Age 5-76 days, 3 premature</td>
<td>None between measurements, 100% O₂ whilst held at inflation pressure</td>
<td>Crs values higher from measurements following high P inflation in both descending and repeated ascending direction. Difference greatest at 13.6 and 20.4 cmH₂O</td>
</tr>
<tr>
<td>Nightingale 1965</td>
<td>Paralysed. 10s inflation to set P (6.8-34 cmH₂O = 5-25 mmHg) passive deflation.</td>
<td>n=34 Age &lt; 6/12 mainly herniae</td>
<td></td>
<td>Crs at 20 cmH₂O = 5.4 ± 1.2 ml.cmH₂O⁻¹ Crs 20 cmH₂O &gt; Crs at 27, or 34 cmH₂O High correlation between Crs and body length</td>
</tr>
<tr>
<td>Reynolds 1966</td>
<td>Paralysed. Pt and Poes measured. Inflation to Vt predicted, passive deflation via pneumotachograph</td>
<td>n=15 Age 3-105 days, (12/15 &lt; 60 days). Inguinal herniae, pyloroplasty.</td>
<td></td>
<td>Some values Crs very low. Mean Crs 2.8 ml.cmH₂O⁻¹. Tidal volume not proportional to weight. = 6ml/kg given. May have influenced Crs values.</td>
</tr>
<tr>
<td>Author and Date</td>
<td>Technique</td>
<td>Parameters measured</td>
<td>Subject group</td>
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</tr>
<tr>
<td>Lunn 1968</td>
<td>Paralysed, Poes and Pao measured. Super syringe inflation, 10 to 40 ml injected</td>
<td>Cl, Ccw, Crs</td>
<td>n=10 Age not given. Height &lt; 5 kg</td>
<td>Manual between measurements</td>
</tr>
<tr>
<td>Sharp 1970</td>
<td>Paralysed. Cuffed tracheal tube. Super syringe VH 10 secs at +40 cmH\text{O}2. Measured at P ≤ 40 cmH\text{O}2, 3-5 second equilibration. Deflated to FRC, V corrected for compression at 6P</td>
<td>Crs at 20 cmH\text{O}2 Inspiratory Crs</td>
<td>n=50 Age 22 months to 18 years</td>
<td>?manual between measurements. 100% O\text{2}</td>
</tr>
<tr>
<td>Fisk 1970</td>
<td>Paralysed, open chest. 6 hyperinflations VH. Super syringe 2-3 aliquots, Ps 20 cmH\text{O}2, 2 seconds equilibration.</td>
<td>Crs both after opening and before closing chest.</td>
<td>n=78 Age &lt; 12 months (42) 1-7 years (36) Thoracic surgery.</td>
<td>N\text{2}O + O\text{2}. Mechanical ventilation</td>
</tr>
<tr>
<td>Author and Date</td>
<td>Technique</td>
<td>Parameters measured</td>
<td>Subject group</td>
<td>Ventilation</td>
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<tr>
<td>Nisbet 1971</td>
<td>Hyperinflation VH. Pre and post paralysis measurements, stepwise inflation and deflation, P ≤ 30 cmH₂O. Crs at FRC and 10% predicted TLC. To obtain normal values for non anaesthetised infants.</td>
<td>Cl, Ccw, Crs</td>
<td>n=40 Age 5-16 years non thoraco-abdominal surgery</td>
<td>O₂ + halothane</td>
</tr>
<tr>
<td>Milner 1972</td>
<td>Intubated paralysed. Inflated jacket for tidal volume, maintained P (compared with super syringe values).</td>
<td>Crs</td>
<td>n=14 Age 7/52 to 5 years.</td>
<td>?gas used. Manual ventilation</td>
</tr>
<tr>
<td>Dobinson 1973</td>
<td>Pre induction FRC. Post induction paralysed FRC by helium dilution. Oesophageal balloons for dynamic Cl.</td>
<td>FRC pre and post induction. Cl post induction. FRC and Cl over operative period.</td>
<td>n=33 Age 5-18 years 19 orthopaedic, 14 cardiac (11/19 + all cardiacs, FRC post induction)</td>
<td>Piston ventilator methoxyflurane + O₂ ± N₂. Tidal volume 10 ml/kg</td>
</tr>
<tr>
<td>Author and Date</td>
<td>Technique</td>
<td>Parameters measured</td>
<td>Subject group</td>
<td>Ventilation</td>
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<tr>
<td>Hatch 1975</td>
<td>Inflated jacket for tidal volume and respiratory frequency.</td>
<td>End expiratory level Crs (Paralysed).</td>
<td>n=15 Age 4 months to 5 years, (13 &lt; 5 years)</td>
<td>Self then IPPV $N_2O_2$ halothane</td>
</tr>
<tr>
<td>Gregory 1975</td>
<td>Helium dilution. Effect of PEEP on FRC post op.</td>
<td>FRC, $P_{O_2}, P_{CO_2}$</td>
<td>n=19 Age &lt; 3 months Post cardiac surgery n=12 FRC. Repeat values up to 48 hrs post operative.</td>
<td>Self ventilation with decreasing $F_{IO_2}$ and CPAP</td>
</tr>
<tr>
<td>Motoyama 1977</td>
<td>Paralysed. Oesophageal balloons. Helium dilution. Forced (negative pressure) expiration from TLC (40 cmH2O). Super syringe inflation.</td>
<td>Crs, FRC, MEFV (Maximal expiratory flow volume).</td>
<td>n=50 Age 2 days to 17 years</td>
<td>?IPPV</td>
</tr>
<tr>
<td>Tusiewicz 1977</td>
<td>Response to $CO_2$ stimulus. Pre and during anaesthesia. Rib cage and abdominal magnetometers. PNT. Inspiratory effort 100 ms after occlusion.</td>
<td>Response to $CO_2$, rib cage motion and diaphragm descent. Inspiratory drive.</td>
<td>n=5 Age 9-18 years orthopaedic surgery</td>
<td>Self ventilation. ± $CO_2$ stimulation</td>
</tr>
</tbody>
</table>
### Author and Date

**Damgaard - Pedersen** 1980

**Technique**
- Computerised tomography (CT) scanning during sedation or general anaesthesia.

**Parameters measured**
- Presence of parenchymal changes during anaesthesia.

**Subject group**
- n=29 anaesthetised
- 43 CT scans; n=52 sedated, 85 scans. Age 4 months to 7 years

**Ventilation**
- IPPV N₂O O₂ (1 ketamine only)

**Results, comments**
- 35/43 scans during general anaesthesia had evidence of parenchymal changes in dependent regions of the lungs. No such changes seen in scans from sedated subjects.

---

**Helms** 1982

**Technique**
- Whole body plethysmography.

**Parameters measured**
- TGV, Rldyn, Cldyn

**Subject group**
- n=23 14 sedated, 9 anaesthetised. Age 3 weeks to 2.5 years

**Ventilation**
- Self ventilating

**Results, comments**
- TGV not influenced by position in anaesthetised infants. Cldyn lower when supine than when in lateral position. Oesophageal balloon Poes:Pm ratio low during occlusion, pleural pressure not necessarily equally distributed (? validity of Cldyn results)

---

**Lindahl** 1984

**Technique**
- Intubated. PNT and gas analysis.

**Parameters measured**
- Tidal parameters.
- CO₂ production and clearance.

**Subject group**
- n=58 Age 1 month to 6 years. Non thoracic surgery

**Ventilation**
- Intubated. Self ventilation N₂O + halothane in O₂

**Results, comments**
- Apparatus resistance of 15 cmH₂O.l⁻¹.s may have influenced results in older children. Tidal volume corrected for weight 5.2 ± 1.2(SD) ml/kg => fresh gas flow should be 2.5 x tidal volume x Weight x frequency or 15 x kg x f to avoid rebreathing in children up to 20 kg. High minute ventilation:CO₂ output in younger infants, inefficiency of ventilation.

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<table>
<thead>
<tr>
<th>Author and Date</th>
<th>Technique</th>
<th>Parameters measured</th>
<th>Subject group</th>
<th>Ventilation</th>
<th>Results, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulse 1984</td>
<td>Intubated, spontaneously breathing and paralysed. PNT and gas analysis.</td>
<td>Tidal parameters. CO\textsubscript{2} production and clearance.</td>
<td>n=22 Age 4 months to 5 years. Non thoracic surgery</td>
<td>N\textsubscript{2}O + 0.5-2% halothane in O\textsubscript{2}</td>
<td>Following opioid pre medication end tidal CO\textsubscript{2} spontaneous ventilation &gt; IPPV. Decrease in wasted ventilation (dead space) during IPPV.</td>
</tr>
<tr>
<td>Hatch 1984</td>
<td>Intubated. PNT and gas analysis.</td>
<td>Tidal parameters. Minute ventilation, CO\textsubscript{2} production and clearance ± Caudal analgesia.</td>
<td>n=26 Age 1-5 years 13 Caudal analgesia lower abdominal surgery</td>
<td>Self ventilation halothane N\textsubscript{2}O O\textsubscript{2}</td>
<td>Respiratory frequency and minute ventilation less in Caudal group. Lower minute ventilation clearing as much or more CO\textsubscript{2} than non Caudal group, =&gt; more efficient ventilation. (Related to lower halothane concentrations).</td>
</tr>
<tr>
<td>Wren 1984</td>
<td>pre and post induction. PNT and gas analysis.</td>
<td>Tidal parameters, minute ventilation. Effect N\textsubscript{2}O on respiration.</td>
<td>n=10 Age 4-11 years 5 papaveretum, 5 thiopentone premedication</td>
<td>Self ventilation N\textsubscript{2}O O\textsubscript{2} halothane. Varying N\textsubscript{2}O concentration</td>
<td>Ventilatory depression reduced as N\textsubscript{2}O reduced NB subsequent work (Wren 1986) demonstrated halothane concentration also to be changing and responsible for ventilatory effects, not N\textsubscript{2}O.</td>
</tr>
<tr>
<td>Shulman 1985</td>
<td>Helium dilution. FRC pre and post ketamine induction.</td>
<td>FRC pre and post</td>
<td>n=9 1 age 10 months, rest 3-6.5 years</td>
<td>Self ventilation Air + helium</td>
<td>FRC changes on induction of anaesthesia varied from +40% to -18%</td>
</tr>
</tbody>
</table>
# Key to Table 1.2

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Cow</td>
<td>compliance of the chest wall</td>
</tr>
<tr>
<td>Cl</td>
<td>compliance of the lung</td>
</tr>
<tr>
<td>Cldyn</td>
<td>dynamic compliance of the lung</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airways pressure</td>
</tr>
<tr>
<td>Crs</td>
<td>compliance of the respiratory system</td>
</tr>
<tr>
<td>FRC</td>
<td>functional residual capacity</td>
</tr>
<tr>
<td>P</td>
<td>pressure (mean airway unless otherwise defined)</td>
</tr>
<tr>
<td>Pao</td>
<td>pressure at the airway opening</td>
</tr>
<tr>
<td>PNT</td>
<td>pneumotachograph</td>
</tr>
<tr>
<td>Poes</td>
<td>oesophageal pressure</td>
</tr>
<tr>
<td>Pt</td>
<td>tracheal pressure</td>
</tr>
<tr>
<td>PNT</td>
<td>pneumotachograph</td>
</tr>
<tr>
<td>TGV</td>
<td>thoracic gas volume</td>
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<tr>
<td>TLC</td>
<td>total lung capacity</td>
</tr>
<tr>
<td>VH</td>
<td>volume history</td>
</tr>
<tr>
<td>R1</td>
<td>resistance of the lung</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>Rldyn</td>
<td>dynamic resistance of the lung</td>
</tr>
</tbody>
</table>

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Section 1 Summary

This Section summarises the state of knowledge regarding respiratory compliance in anaesthetised infants at the inception of this thesis.

1 Although whole body plethysmography and oesophageal manometery had become the established methods for measuring respiratory mechanics in infants, until recently there was no technique available which required relatively uncomplicated equipment and was simple to apply to the non-apnoeic infant.

2 With the introduction of the "occlusion techniques", total respiratory compliance and resistance could be studied in both spontaneously breathing infants and those requiring assisted ventilation. One technique could now be applied to the same infant whether sedated, anaesthetised, or anaesthetised and paralysed.

3 Inhalation anaesthesia had been shown to result in a decrease in lung and total compliance in adults, and a reduction in FRC in both adults and children. No such measurements in infants had been reported.

4 Potential contributors to these changes in FRC and compliance included changes to thoracic blood volume, the position and function of the diaphragm, changes in chest wall tone, and altered surfactant secretion or function.

5 Large lung inflations were found to have a marked effect on measured values of compliance both in adults and animals.

6 As inflation volumes appeared to influence compliance measurements, values from anaesthetised paralysed infants may not have been appropriate reference values for infants with lung disease (in the non anaesthetised state).

7 The many differences between the adult and the infant respiratory systems made it inappropriate to extrapolate, without verification, findings in adults to infants. This included the reduction in compliance which occurred following the induction of anaesthesia.

8 With increasing use of compliance measurements to monitor clinical progress in ventilated infants and neonates, there was an urgent need to investigate the role of tidal volume in determining measured Crs in the younger patient.
Aims and objectives of the current research.

To test the following hypotheses:

1 Total respiratory compliance (Crs) is reduced during halothane anaesthesia in infants and young children. This had previously been demonstrated in adults but not infants.

2 During halothane anaesthesia, values for Crs obtained when spontaneously breathing are not interchangeable with those obtained during assisted ventilation in the same infant.

3 Measurements of Crs in anaesthetised paralysed infants are directly influenced by the pattern of ventilation administered during measurements.

4 Data collection and analysis for the MOT can be achieved more efficiently by replacing analogue recordings and manual analysis with computerised data collection and computer assisted analysis.

At the inception of the research described in this thesis, there had been no reports of the multiple occlusion technique (MOT) being applied successfully to the anaesthetised infant or young child. The first objective of this research was therefore to evaluate the suitability of the MOT for measuring Crs in anaesthetised infants, both during spontaneous breathing and when paralysed, receiving assisted ventilation.

In view of the increasing interest in tidal breathing parameters and multiple analyses of data, computerisation offered the necessary ability to handle large amounts of raw and derived data. It was hoped that computerisation would in turn widen the use of the technique improving both its application, and clinical interpretation of data so obtained.
Section 2

Equipment and Methods

Definitions
A session in which Crs was measured is referred to throughout as 'measurement' or 'measurements'.
P represents pressure at the airway opening, V volume (inflation/deflation or tidal), and \( \dot{V} \) flow. \( \delta P \) generally refers to equilibrated airway pressure during an occlusion (plateau pressure), \( \delta V \) occluded volume above end expiratory level (EEL).

Respiratory mechanics - a brief summary of the principles involved
Compliance is an expression of the elastic recoil of the respiratory system, defined as the change in unit volume for a given change in pressure, expressed in ml.kPa\(^{-1}\).
In the absence of muscle activity, total compliance of the respiratory system (Crs) is determined solely by the relationship between outward recoil of the chest wall and the inward recoil of the lung. At true relaxed, passively determined, end expiratory lung volume, these must be equal and opposite. Chest wall compliance incorporates the contribution of the diaphragm and abdomen as well as the rib cage.
Lung compliance is determined principally by the number and type of elastic and collagen fibres of the lung tissue and the surface tension forces at the gas - liquid interface of the alveoli. In disease states, an increasing contribution may be made by changes in pulmonary blood volume, interstitial lung fluid, and vascular smooth muscle. As the chest wall and lung are arranged in parallel:

\[
\frac{1}{Crs} = \frac{1}{Cl} + \frac{1}{Ccw}
\]

where Crs = total respiratory compliance, Cl = lung compliance  
Ccw = chest wall compliance

Rohrer in 1915 noted that in the absence of airflow and muscle activity, alveolar pressure would be equal to airway pressure and equal and opposite to the static elastic pressure of the total respiratory system, i.e.

\[
P_{alv} = P_{pl} + P_{el}
\]

where P = pressure, alv alveolar, pl pleural, el lung elastic recoil.
If the airway is occluded, and total relaxation ensured, the pressure resulting at the airway opening, equilibrated with alveolar pressure, can be measured. Compliance is measured by relating the change in volume to the change in pressure of the closed system, with reference to volume and pressure at atmospheric pressure:

\[ Crs = \frac{\delta V}{\delta P} \]

where \( \delta V \) = volume above lung volume at atmospheric pressure (FRC)

\( \delta P \) = pressure change from atmospheric to equilibrated airway/alveolar pressure

This relationship only holds in the absence of any respiratory effort.

The equation of motion of the respiratory system states

\[ P_{app} = P_{el} + P_{res} + P_{inert} \]

where \( P \) = pressure, \( app \) = applied, \( el \) = elastic forces, \( res \) = resistive forces, \( inert \) = inertive forces.

Inertive forces have historically been considered to be negligible, although more recently these have been receiving greater interest (Turner 1991). Thus the pressure applied to the respiratory system during inspiration has to overcome primarily the pressure resulting from elastic and resistive forces.

During passive expiration, in the absence of muscle activity,

\[ P_{app} = 0. \quad \text{Thus} \quad P_{el} = -P_{res}. \]

Since

\[ Crs = \frac{\delta \text{Volume}}{\delta P_{el}} \quad \text{and} \quad Rrs = \frac{\delta \text{Pres}}{\delta \text{Flow}} \]

where \( Rrs \) is total respiratory resistance i.e. chest wall, lung tissue and airways resistance.

By substitution

\[ \frac{\delta \text{Volume}}{\delta \text{Crs}} = -Rrs \times \frac{\delta \text{Flow}}{\delta \text{Crs}} \]

Thus in the passive state

\[ \frac{\delta \text{Volume}}{\delta \text{Flow}} = -\text{Resistance} \times \text{Compliance} \]

Since \( \frac{\delta \text{Volume}}{\delta \text{Flow}} = -\text{Time} \quad \text{or} \quad -\text{Trs} \)

where \( \text{Trs} \) = time constant of the respiratory system;
this is therefore the slope of a passive flow volume curve. Knowing $\text{Crs}$ or $\text{Rrs}$ and the expiratory time constant of the respiratory system ($\text{Trs}$) the third parameter may be computed.

i.e. knowing $\text{Crs}$ and $\text{Trs}$, $\text{Rrs}$ may be calculated from $\text{Crs} \times \text{Rrs} = \text{Trs}$. 
Section 2.1

Equipment characteristics

Introduction
The performance characteristics of physiologic measurement apparatus can be divided into static, dynamic, and physiologic. Static characteristics include linearity of response, hysteresis, and baseline stability, and apply to the static, or very slowly changing state or signal. Dynamic characteristics, on the other hand, relate to the rapidly changing state and include frequency response and phasing of the signals. Physiological reactance describes the influence of the recording system on the physiological event itself, such as the increase in nasal resistance resulting from the nasal introduction of an oesophageal catheter or balloon.

Static characteristics

Linearity of response
The equipment should have a linear response to incremental changes in input over the range of measurements being studied, i.e. doubling the input signal should result in a doubling of the response. In practice, the linearity of a measurement system is assessed in the 'as used' configuration since, especially for flow devices, great changes occur as a result of altered configuration. To assess linearity a known signal is applied and the response recorded. Incremental increases or decreases in the input are similarly applied and the resulting responses plotted against the known inputs. The linear regression line through these points should be a perfect fit (correlation coefficient $R^2 = 1$), and pass through the origin (zero input => zero output).

In practice most measuring equipment has a linear range, beyond which the relationship does not hold, and is chosen such that the linear range of the device covers the whole range of measurements being made but does not necessarily extend beyond this.

Baseline stability
Currently available transducer systems are constructed to have extremely stable baselines, dependent only upon atmospheric changes, although a heating effect may be seen if electronic equipment is not brought to a stable functioning temperature before use.
Dynamic characteristics

Frequency response

In any pressure measuring system there are three components, the transducer, pre amplifier and recorder. Differential pressure transducers, as used in this study, consist of a diaphragm which is displaced in direct proportion to the pressure applied. This results in an electrical signal proportional to the degree of displacement. The characteristics of such a transducer depend upon the plasto elastic properties of the diaphragm, the dimensions of the transducer chambers, and the properties of the material filling these chambers. In addition, the characteristics of the probe carrying the signal to the transducer need to be such that minimal distortion of the signal occurs during transmission from source to transducer. For minimal distortion of such a signal the following are essential:
1. a uniform probe to prevent wave reflections from points of transmission,
2. a large probe radius, stiff probe wall, slow transmission velocity and low compressibility to ensure equal attenuation of frequency components,
3. low frictional properties of the probe to ensure equal transmission of component frequencies, and
4. stabilisation of the probe - preventing movement artifact.

In an air filled transducer system, the low density but high compressibility of the gas can result in marked attenuation of the signal if the volume within the probe and transducer chamber is too large and gas compression occurs as increasing pressure is applied.

When subjected to a change in pressure, the transducer diaphragm responds by oscillating in simple harmonic motion. With no resistance to movement, or damping, these oscillations would continue at a constant frequency, known as the natural frequency of the system. The degree of damping, which causes these oscillations to stop, and the natural frequency of the system, together determine the frequency response of the system. This determines the range of frequencies over which the transducer system will accurately record both the amplitude and the phase of any signal. As the frequency of a given signal input (of unchanging amplitude) increases, so the amplitude of the recorded output is attenuated. Accurate recording of physiological events require that the signals fall within the bandwidth of the transducer - amplifier - recording system, i.e. that portion of the frequency response curve which is essentially flat.

Critical damping of the signal is that degree of damping which is just sufficient to abolish overshoot, but causes the system to reach stability in
the shortest possible time (Fig 2.1).

For measurements of respiratory parameters, it has been shown that the measurement system should have a uniform frequency response to the 10th harmonic of the fundamental frequency. In infants, the fundamental frequency, in this situation respiratory rate, is usually below 1 Hz, thus the system must have a satisfactory dynamic range of at least 10 Hz.

**Phasing**
The delay between the signal input and signal output is the phase lag, and for faithful recordings this must be the same at all frequencies. In addition, where two or more transducer systems are being recorded simultaneously, all should have exactly the same degree of lag. If they are out of phase with one another when subjected to the same signal input, no comparison can be made between recordings of different signals, such as airflow and airway pressure.

**Physiologic considerations.**
Physiological events or parameters may be modified by the introduction of measurement apparatus. The normal configuration and relationship between structures may be altered, and the presence of the apparatus may distort the very physiological changes it is to measure.
If the volume within which pressure changes are to be measured is increased by the capacity of the probe - transducer system, the resulting pressure changes may not reflect those naturally occurring in the absence of such apparatus.
In infants, oesophageal pressure measuring devices, used to measure lung resistance, will significantly alter airway, and thus, total resistance if passed nasally. This is a result of physically reducing the airway lumen in the infant breathing nasally. Similarly, the application of a face mask has been shown to alter tidal breathing parameters, and such changes must be considered when interpreting measurements using such equipment.

The equipment used in this study was assessed for the ability to record faithfully the events under investigation, and where possible was designed to minimise the influence of the equipment on the parameters under investigation.
The following section describes the physical characteristics and behaviour of the apparatus used to measure Crs in this study.
Figure 2.1 Critical damping of transducer signal. Critical damping prevents overshoot of the signal but results in equilibration in the shortest possible time. Solid line: input signal. Broken line: recorded signal -
A. undamped, B. underdamped, C. critically damped, and D. overdamped.
Section 2.2

Measurement apparatus

For the measurement of Crs using the multiple occlusion technique, the following were required:
1. Measurement of pressure at the airway opening (P), and tidal volume (V).
2. Rapid occlusion of the airway opening, with the occluding device defaulting to the open (unoccluded) position.
3. A patient circuit which allowed the administration of special gases, such as O₂ and N₂O, during measurements.
4. Visual display in real time of P and V for timing occlusion.
5. Recording system with rapid response, which allowed retrospective inspection and analysis of data.

These could be divided into two units, 1. the patient circuit, and 2. the display and recording system.

Patient measurement system

Fig 2.2a, 2.2b

This was comprised of 4 components parts:
- shutter (airway occluder)
- pneumotachograph
- anaesthetic reservoir bag with t-piece and tubing
- tracheal tube connector or face mask

Shutters

Two types of shutter were developed and used in this study.

Specifications

Dead space and disturbance to airflow should be minimal. The occluding mechanism should incorporate a fail-safe return to the open, unoccluded, configuration. There should be a pressure port to sample pressure between the shutter and the infant's airway, i.e. pressure at the airway opening, P.

Design 1  Fig 2.3

This design had a dead space of 3 ml as used in the infant system, and a resistance to airflow of 0.0147 kPa.l⁻¹.s (flow - 400 to + 400 ml.s⁻¹).

Designed to give rapid response closure using a standard cable release, this shutter design also featured spring loaded return to the open position. This shutter had 2 advantages over the subsequent design.
Figure 2.2a  Apparatus for measuring Crs in intubated infants requiring supplemental oxygen or anaesthetic gases to be administered. Shutter design 2 shown.

Figure 2.2b  Apparatus for measuring Crs in spontaneously breathing infants requiring no supplemental oxygen or anaesthetic gases. Face mask shown attached to shutter design 2.
1. The dead space could be minimised during non recording periods by diverting the fresh gas flow from the t-piece to the inlet between the shutter and the infant. This eliminated all of the added dead space due to the pneumotachograph, and reduced that of the shutter by 2 ml.

2. With the occluder block operating at 90° to the direction of airflow, flow disturbance was minimised when the shutter was open since the system from the infant connector to the anaesthetic reservoir bag followed a straight line.

Operational disadvantages resulted in redesign of the shutter:-

1. Sterilisation of the shutter was problematic. Low temperature autoclaving caused deterioration of the springs and distortion of the occluding block. These in turn resulted in deterioration in the performance of the shutter, failing both to occlude the airway effectively, and to return to the fully open position on release. By replacing autoclaving with alcohol immersion following ultrasonic cleaning, these problems were partially overcome.

2. The smallest deposits of debris within the shutter mechanism prevented an airtight seal during airway occlusion. This resulted in the shutter being removed from service whilst it was dismantled, cleaned, resealed, and sterilised, all of which required a minimum of 24 hours.

3. In addition to the strong spring required to ensure that the shutter returned to the fully open position on release of the cable, spring loading of the occluder block against the plane of airflow was necessary to effect an airtight seal. The force required to overcome these combined spring forces, in order to close the shutter, proved excessive for the standard cable releases used at the beginning of the study. These were therefore replaced by purpose-made plungers which in turn required considerable effort from the operator.

The fine balance between these and the ease with which the seal was lost due to changes in the spring tensions or alignments resulted in unacceptable levels of shutter failure due to leaks, despite the introduction of the solid rod plunger to push the occluding block across inside the shutter.
**Figure 2.3** Shutter design 1 shown in the occluded position. Occluding mechanism at $90^\circ$ to patient connector. Reduced dead space fresh gas inlet designed for use between measurements, bypassing pneumotachograph.

**Figure 2.4** Shutter design 2 shown in the occluded position. Note occluding mechanism is in the same plane as the patient connector. Reduced dead space fresh gas inlet no longer incorporated into shutter design.
Design 2  Fig 2.4
The dead space of this design was 5.5 ml, including connectors, and
resistance to airflow was 0.04 kPa.l⁻¹.s (flow -400 to +400 ml.s⁻¹).
By rotating the moving part of the shutter through 90°, to be in the plane
of the patient connection (see Fig 2.4), minimal force was required to close
the shutter and the spring mechanism which re-opened the shutter (on release
of an occlusion) had much less resistance to overcome. Standard camera
cable release mechanisms could now be used to operate the shutter
mechanism.

Potential disadvantages of shutter design 2
The increase in dead space, of 2.5 ml with respect to design 1, was not of
significance in most studies. However, in the neonate or severely
compromised small infant with a tidal volume of less than 15 to 20 ml,
considerable rebreathing would occur. All infants described in this study had
tidal volumes greater than 25 ml unless receiving a fresh gas flow of
increased FiO₂, thus the increased dead space was not a problem in the
measurements reported in this thesis. Despite the fresh gas flow, some
small degree of CO₂ retention cannot be excluded in the infants with very
small tidal volumes, particularly infant AS (table 3.10).
The introduction of an angle of approximately 110° into the previously
straight system was expected to cause turbulence to the airflow, with a
consequential increase in apparatus resistance. However this increased by
only 0.025 kPa.l⁻¹.s. The effect on the linearity of the Fleisch
pneumotachographs, of receiving a slightly turbulent rather than more linear
flow (as delivered by the straight - through shutter design) was insignificant.
See below - pneumotachograph.

The respiratory gas inlet for minimising dead space had proved of very
limited use. Only on rare occasions were infants left connected to the
system when measurements were not actually being taken. The smaller
infants studied, who may have required a reduced dead space, also invariably
required assisted ventilation. Thus, this port was excluded from the design
as rarely used and a potential source of air leak.
This shutter was designed to tolerate low temperature autoclaving which was
successfully utilised between each infant.

Prior to every measurement, the shutter was connected to the transducer and
water manometer, occluded, and tested to ensure it could withstand a
pressure of 20 cmH\textsubscript{2}O (\approx 2kPa) without leaking, detected as a fall in pressure with time.

**Pneumotachograph**

The basic principle behind the pneumotachograph is that the pressure drop across a flow resistive device is directly proportional to the flow through it. i.e. for a laminar device

\[ \delta P = \dot{V} k \]

where \( \delta P \) is the differential pressure
\[ \dot{V} \] flow rate
and \( k \) a factor incorporating both the viscosity and density of the gas

i.e. \( \delta P = \frac{\dot{V} 8l \mu}{\pi r^4} \) from Poiseuille's law: \[ V = \frac{(P_1 - P_2) \pi r^4}{8l \mu} \]

Where \( l \) is tube length \( r \) tube radius \( \mu \) viscosity of the gas

The Fleisch pneumotachograph is comprised of a network of fine capillaries which both laminarise the flow passing through the device, and act as the resistive element.

Because of the dead space to resistance ratio of the Fleisch design, two different sizes of pneumotachograph were used for different sized infants. Selection was based on three factors:
1. the range of linearity of the pneumotachograph when in the measurement system (increases with larger sized pneumotachographs),
2. the dead space of the pneumotachograph (increases with increasing size),
3. the resistance of the pneumotachograph (decreases with increasing size).

For the greatest sensitivity, the smallest pneumotachograph which remained linear throughout the range of flows being measured was selected for each infant (subject to the limitations of the original recording equipment, see below). This also had to take into account the resistance to flow and any effect this may have had on the infant's ventilation.

Thus for a young infant of 4 kg body weight, with peak flow rates of \(< 200\text{ ml.s}^{-1}\), a size 0 pneumotachograph was selected.

The linearity of this pneumotachograph, as used in the measurement system, was true to \( \pm 250 \text{ ml.s}^{-1} \) flow, and the dead space and resistance of the apparatus in this configuration were 7 ml and 0.48 kPa.l\textsuperscript{-1}.s respectively.

**Gas viscosity**

From the equation above, the differential pressure, \( \delta P \), across a
pneumotachograph at any given flow rate is directly proportional to the viscosity of the gas (\( \mu \)).

In this study the gases used, and their respective viscosities at 20°C were:
- Air 182.0 \( \mu P \) for measurements on sedated spontaneously breathing infants.
- \( O_2 \) 203.5 \( \mu P \) for anaesthetised and sick infants.
- \( N_2O \) 145.5 \( \mu P \) for anaesthetised infants.

1 Poise (P) = 0.1 Pa.s

It was therefore essential that calibration of the system was performed using the appropriate gas mixture, as used during measurements. Fig 2.5 illustrates the effect on the uncalibrated signal size of varying \( O_2 \) concentration. Gas temperature and the presence of water vapour also influence the resulting viscosity of a gas mixture. Heating the inspired gas as it passes through the pneumotachograph may compensate in part for the difference between inspired and expired gas temperatures (Turner 1989, Miller 1986, Grenvik 1966).

Any variability caused by temperature changes or by the difference in composition between inspired and expired gases due to respiration are not normally corrected for when using this type of device. It is probable that opposing differences tend to minimise any overall change in calibration characteristics since inspired and expired tidal volumes do not show a continual drift in either direction, suggesting that the calibration using dry air or \( O_2 \) mixture is still appropriate (Grenvik 1966).

![Flow Gain Graph](image)

**Figure 2.5** The effect of oxygen concentration on the size of the uncalibrated flow signal. For the same flow (measured using appropriate rotameters) signal size increases with oxygen concentration.
The capillary type of pneumotachograph has been shown by Funicane to have a more linear relationship with flow than the screen type, in which a gauze type thin screen acts as the resistive element between two pressure ports (Funicane 1972). Screen pneumotachographs have the advantages that dead space can be minimised, the resistance to airflow is less, and the signal is not so dependent on receiving a laminar flow as the capillary type (Fleisch) pneumotachograph.

However, the improved linearity across a wider range of flows, proven stability of signal, robust design, and availability of low flow ranges, made Fleisch the pneumotachographs of choice for this study. These pneumotachographs have been demonstrated to be sensitive to the wave form of the applied flow (Funicane 1972). The apparatus was therefore always calibrated as used during measurements, with pneumotachograph, shutter, and connectors in place.

To avoid the problems of phase lag, signal attenuation, and inadequate frequency response of the pneumotachograph and transducer system (see below), semi rigid (i.e. very low compliance) 3.00 mm internal diameter vinyl tubing of exactly equal lengths were used to join the pneumotachograph pressure ports to the transducer connectors. This also ensured that the coefficient of displacement was identical on both sides of the pressure transducer (Dezateux 1991).

The physical characteristics of the size 0 and size 1 Fleisch pneumotachographs are listed below:

<table>
<thead>
<tr>
<th></th>
<th>Dead space</th>
<th>Resistance at 100 ml.s^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>size 0</td>
<td>2.5 ml</td>
<td>0.43 kPa.l^{-1}.s</td>
</tr>
<tr>
<td>size 1</td>
<td>10 ml</td>
<td>0.10 kPa.l^{-1}.s</td>
</tr>
</tbody>
</table>

The characteristics of the combined pneumotachograph, transducer, and amplifier system, were such that a tidal volume of >100 ml was difficult to accommodate on the paper recording, the resulting signal size being ≈12 cm on 15 cm wide paper. With the original amplifier - transducer system it was therefore necessary to use the Fleisch size 1 pneumotachograph for infants of ≥ 6 kg body weight.

**Linearity of response**

The linearity of responses of the Fleisch sizes 0 and 1 pneumotachographs were measured in turn, as used in the infant system. All three gases were assessed, air, O₂, and N₂O. Fig 2.6 shows the linearity signal of a size 1 pneumotachograph as used with air. All apparatus configurations,
Figure 2.6  Linearity of Fleisch size 1 pneumotachograph. Measured using air, for both gains of original amplifier (Section 2.2).

Figure 2.7  Linearity of Volume signal (electronically integrated flow), Fleisch size 1 pneumotachograph. As input (V) doubles, so does output (cm paper deflection).
incorporating either size 0 or 1 pneumotachograph, gave linear responses in both inspiratory and expiratory directions of flow throughout the range of flows measured in the infants.

Volume linearity was measured up to 100 ml. Since this depended primarily on the flow rate of the delivered input remaining within the linearity of the pneumotachograph under examination, frequency dependence for a given volume would be expected since this implies increasing flow rates.

The linearity of volume using the size 1 pneumotachograph and air, with a frequency of input of \( \approx 1 \text{ Hz} \), is illustrated in Fig 2.7.

Pneumotachographs were low temperature autoclaved initially. As this was found to be unduly stressing the electrical wiring, alcohol immersion was used to achieve sterilisation (70% alcohol).

Linearity of the recordings from the airway pressure transducer system were assessed in the same way as for the pneumotachograph, and found to be totally linear within the range of pressures applied (± 40 cmH\(_2\)O or 3.93 kPa).

**Anaesthetic reservoir**

A 1 litre anti-static neoprene - dipped anaesthetic bag and T-piece were connected to the distal end of the pneumotachograph. A fresh gas flow of 6 l min\(^{-1}\) was supplied to the T-piece during measurements which required the administration of O\(_2\) enriched or anaesthetic gases. 4 l min\(^{-1}\) fresh gas flow has been recommended as the minimum required to prevent rebreathing of expired gases in this age group (Lindahl 1984).

The reservoir bag and T-piece were disinfected in cold solution by the hospital CSSD.

**Connectors**

All components of the system were connected with standard or purpose made adaptors, minimising dead space and preserving the laminar nature of the lumen of the whole system as far as possible. Appropriately sized Oxford connectors, 15 mm Portex or Cardiff connectors with anti-static black rubber tubing were used to connect the apparatus to tracheal tubes. Face masks required purpose made adaptors to the shutter. The size 0 pneumotachograph was inserted into the shutter body and end of the T-piece; the size 1 pneumotachograph having external wide lumen connectors to both shutter and t-piece. All connectors were sterilised in sodium hypochlorite solution or autoclaved.
The completed infant system, with the Fleisch size 0 pneumotachograph (PNT), as used in measurements had the following characteristics:

<table>
<thead>
<tr>
<th>Resistance at 100 ml.s(^{-1}) (kPa.l(^{-1}).s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNT alone</td>
</tr>
<tr>
<td>Shutter design 1</td>
</tr>
<tr>
<td>Shutter design 2</td>
</tr>
</tbody>
</table>

The pressure flow characteristics of the apparatus as used for anaesthetised infants are shown in figs. 2.7a and 2.7b.

**Figure 2.7a** Pressure - flow relationship for the apparatus (Figure 2.2a) as used. Fresh gas flow = 5 l.min\(^{-1}\), shutter designs 1 and 2. Size 0 pneumotachograph.

**Figure 2.7b** Pressure - flow relationship for the apparatus as used. Fresh gas flow ≈ 5 l.min\(^{-1}\), shutter designs 1 and 2. Size 1 pneumotachograph.
Figure 2.8  Breathing system, signal display and recording layout. Shutter design 1 (with facility for reduced dead space fresh gas flow). X-Y plotter removed for measurement sessions. See also Fig 5.1 (Section 5).
Display and recording system
See breathing system layout, Fig 2.8.

Transducers
Linearity of response for the complete system was assessed, and found satisfactory, as described above. The frequency response and phasing of the signals for the system as a single entity are described below. The shutter pressure port (P) and pneumotachograph pressure ports (V) connected directly with semi-rigid tubing to pressure sensitive air filled transducers. P was initially measured using a Gould dome transducer. This was later upgraded to the more robust Validyne MP45 ± 50 cmH₂O differential pressure transducer. The reference pressure for this transducer was atmospheric pressure. The pneumotachograph was connected to the two sides of an MP45 ± 2 cmH₂O transducer.

Signal conditioning and amplification
Both transducer outputs were conditioned during the initial months of the study (i.e. from infant 1 to infant 69) by a purpose built amplifier and integrator unit. The original amplifier had a 20 Hz high frequency cut-off and, being DC, effectively no low frequency cut-off (i.e. was not time constant dependent).
This system became increasingly unstable with time so was replaced with Validyne modular conditioning units (CD 19A carrier demodulators in an MC1-3 carrier unit) and integrator (FV156). The pneumotachograph output was amplified directly to give airflow, and integrated to give tidal volume. All signals were then filtered at 25 Hz (greater than 10 times the maximum expected respiratory frequency) and output to display and recording equipment.

Racal tape recorder
To permit play back of real time data onto an oscilloscope and plotter, all signals were recorded on a four channel magnetic tape recorder. This remained in use until computerised collection of data was established (see Section 5).
At the tape recorder input junction, the signals were distributed to the ultraviolet light recorder (S E Labs) and a real time display and storage oscilloscope (Tektronix).

SE Labs, series 3000 ultraviolet light recorder
With rapid response and a full beam deflection of 6" available for each signal, light beam recordings were used to obtain the permanent record of
each measurement at the time of data collection. Following attenuation to
match the signal full scale deflection with the UV scope galvanometers
range, the signals were recorded onto UV sensitive paper (Kodak type 1830).
Recording paper speed was 20 or 50 mm per second, except for calibration
when this was halved (10 mm per second).

**Tektronix 5223 digitising oscilloscope**

This oscilloscope fulfilled 3 major functions. At the time of study, real time
display of tidal volume and airway pressure provided continuous monitoring of
the infant's ventilatory state both quantitatively and qualitatively. This was
of particular value when studying the anaesthetised or sick infants when
immediate response to observed changes may have been required.
The tidal volume display was used to time the expiratory airway occlusions
and, by careful matching of the scopes, to monitor when signals were outside
the limits of the paper recording. Matching the signals allowed instant
changes in amplification to be made to ensure as large a signal as possible
was recorded. Thus, accuracy of subsequent analyses was as great as possible.
Prior to every measurement the matching of the signals between oscilloscope
and UV recorder was assessed to ensure all data displayed on the Tektronix
oscilloscope was within the recording range of both the Racal tape and the
UV recorders.

The third use of the scope utilised its store and plot facility. Recorded
signals played back through the Racal tape recorder could be frozen on
screen in either time base or in the form of X-Y plots. Occlusions and tidal
ventilation could therefore be reviewed at a greater amplification than may
have been possible to record on paper, and X-Y plots downloaded onto an X-
Y plotter to obtain a hard copy. This latter facility was retained until
computerisation was complete.

**Frequency response**
The frequency response of the transducer, amplifier, and recorder system was
assessed by exposing both transducer probes (one side of flow and airway
pressure transducer tubings) to a step input signal, generated by bursting a
balloon within a closed container. The rise time of the resulting signal, the
magnitude of overshoot, and the frequency of the damped oscillations can be
computed to obtain the frequency response of the system. This is described
in detail by Fry in a classic description of the mathematical considerations
required when measuring physiological parameters (Fry 1960), and is therefore
not reproduced here. The frequency response of the system used in this
study was greater than 10 Hz.
Phasing of signals
The importance of recorded signals being in phase with the signal input is mentioned above and is also discussed in detail by Fry. Of even greater importance, when retrospectively analysing data, is that multiple signals being recorded simultaneously should have no phase difference between them. A slight phase shift between signal input and signal recording cannot be prevented due to the time required for the signal to pass through the system, physical or electrical. This phase lag with the signal input must be the same for all recorded signals, and additional damping may be required to bring all recorded signals into phase with each other.

To assess the phasing of the two transducer systems, the connecting tubing from one side of each was fed into a closed bottle. By balloon burst, as for measuring the frequency response, a step input signal was given to both transducers simultaneously. The resulting signals were recorded onto the UV paper running at 100 cm.s^{-1}, and also held on the oscilloscope screen. Both signals achieved peak amplitude simultaneously. Since no difference in phasing was measurable even at this rapid recording rate, the signals were therefore taken to be in phase (Dezateux 1991).

Phasing between signals was checked whenever any changes were made to the system, including changing transducers or transducer tubing.

Calibration of equipment
Calibration was performed for every measurement to allow for slight fluctuations in signal output size and correct for gas mixtures used. Although the signal output remained very stable, particularly once the transducer - amplifier - integrator system was entirely Validyne, regular calibrations were considered vital to identify immediately any developing fault with the system or electronics.

To reduce problems of electronic instability, the equipment was always given the maximum time available to reach thermal equilibrium prior to a measurement session. If necessary a period of pre-warming within the laboratory or ward was used to overcome the problems of limited access time in theatre anaesthetic rooms. This entailed switching the power on to all the units to allow the electronics to warm and the pneumotachograph to be heated.

Known signal calibration was performed for every measurement, at the place of measurement, except in exceptional circumstances (when used in the cardiac catheter laboratory or anaesthetic room, subsequent cases sometimes prevented immediate on site calibration). Calibrated rotameters and a water
column manometer were incorporated into the equipment trolley, thus calibration signal inputs were standard throughout all measurements. Known signals were included in the recordings (paper, tape, computer) for all Crs measurements.

**Airway Pressure**

**Standard signal:** 20 cm of water by column displacement.

**Method**

Transducer tubing from the shutter pressure port was attached directly onto the side of a U shaped water filled manometer via a 3-way tap. With the system open to atmosphere (i.e. transducer reference zero = atmospheric pressure) a short recording was made of this pressure baseline, and the vernier scale adjusted such that the bottom of the water column meniscus read zero. By attaching a syringe to the 3rd port on the tap, the system was closed to atmosphere on the transducer side and air was injected until a positive pressure of 20 cmH₂O was reached. A short recording was made of this signal, then the syringe removed abruptly to ensure the input re-zeroed correctly.

Pressure calibration was thus: \[
\frac{20 \text{ cmH}_2\text{O}}{\text{cm paper}}
\]
giving cmH₂O per cm paper for P signal displacement.

Care was taken to prevent debris entering the water column. The water tubing was periodically cleaned and refilled with fresh sterile water to ensure constancy of the signal.

**Flow**

Although this thesis was concerned with compliance measurements by the multiple occlusion technique, the flow, volume, and pressure signals being recorded were also those required for the single breath (or passive flow volume) technique for measuring Crs and Rrs, if taken from an end inspiratory occlusion.

The flow signal was recorded and calibrated for every measurement both to provide a means of assessing the stability of the system and to permit retrospective examination of calibrated flow volume data if required.

**Standard signal** 6 l.min⁻¹ of the inspired gas used for the measurement, or appropriate mix (e.g., N₂O + O₂).
Method
Calibrated flow meters for oxygen, air and nitrous oxide were used alone, or in parallel with appropriate wide-bore Y connectors if necessary, to deliver the correct gas mixture directly to the patient end of the system. With the transducers connected into the system, the anaesthetic bag (if used during the measurement) open to atmosphere, and no flow through the system, zero flow was recorded. 6 l min\(^{-1}\) of the appropriate inspired gas were then delivered to the patient end of the system. This was recorded for a few seconds before repeating a recording at zero flow.

Flow calibration was thus: \[
\frac{6 \text{ l.min}^{-1}}{\text{cm paper}}
\]
giving l.min\(^{-1}\) per cm paper for flow signal displacement.

During some clinical, and all theatre measurements, the fresh gas flow was supplied to the T-piece at the distal end of the apparatus at an approximate flow rate of 6 l.min\(^{-1}\).

Because of the logistic difficulties of both calibrating the pneumotachograph with the appropriate gas mixture and at the same time administering the mixture as a fresh gas flow of 6 l.min\(^{-1}\), any influence this may have had on the calibration was examined in detail in vitro. Since the influence on the resultant calibration factors was negligible, subsequent calibrations were completed without the fresh gas flow to the T-piece.

Volume
Standard signal 50 ml, 20 ml for infants < 4 kg, of appropriate inspiratory gas mix.

Method
To reduce the level of circulating N\(_2\)O and O\(_2\), volume calibration was performed using a small reservoir of the appropriate gas mix stored in the anaesthetic bag. Using a 50 ml stoppered syringe, the effect this may have had on calculated results was measured using air, O\(_2\), and N\(_2\)O with O\(_2\). No measurable difference in calibration was found between pumping the gases into and out of a closed reservoir bag containing just over 50 ml (to prevent compression effects) but no fresh gas flow, and pumping the same volume through the shutter and pneumotachograph with the bag open to atmosphere and a fresh gas flow of 6 l min\(^{-1}\).

Volume calibration was thus: \[
\frac{50 \text{ ml}}{\text{cm paper}}
\]
giving ml per cm paper.
Section 2.3

Application of equipment

Introduction

The apparatus described in the previous section was designed specifically to perform Crs measurements both in infants requiring assisted ventilation and those who did not. Non-intubated infants were measured during spontaneous breathing, usually following sedation with triclofos. Such measurements were performed both for clinical purposes (usually prognostic) and research (preceding induction of anaesthesia). Intubated infants also fell into the two categories, research or clinical.

If at all possible, clinical measurements of Crs were made with the infant breathing spontaneously, with an increased Fi\textsubscript{O}\textsubscript{2} if necessary. Where this was not possible, relaxation was encouraged by a period of hyperventilation or with sedation, and measurements made during a period of manual ventilation.

Research measurements of Crs were made in intubated anaesthetised infants who were either breathing spontaneously or who were manually ventilated when paralysed following neuromuscular blockade.

In all measurements the infants were lying supine, with neck slightly extended into a neutral position, supported with sand bags if necessary. Measurements for diagnostic or prognostic information from infants with respiratory disease are referred to throughout as 'clinical' measurements.

Sedated infants

Measurements were made following sedation with triclofos sodium according to the following schedule: those under 3 months of age 50 mg.kg\textsuperscript{-1}, between 3 and 9 months 75 mg.kg\textsuperscript{-1} and those over 9 months old 100 mg/kg body weight. The infants were left until sleep was well established and gross body movements had ceased, before measurements were attempted.

Therapeutic putty (Carters, Wiltshire) was placed as a fine rim around an appropriately sized Rendell - Baker face mask (0,1, or 2) which was then connected to the measuring apparatus (Fig 2.2b). Infants not requiring supplemental O\textsubscript{2} were measured without the anaesthetic reservoir bag and T-piece connected. Infants requiring supplemented O\textsubscript{2} were supplied with an appropriately mixed fresh gas flow into the T-piece, this and the anaesthetic bag being connected onto the pneumotachograph (see clinical
measurements, below).

After re-zeroing the integrator with no flow through the pneumotachograph, the face mask was gently applied to the infant's face, ensuring minimal pressure was placed on the bridge of the nose and the nares. Supporting the mask at chin and cheeks, the tidal volume trace was observed for a reproducible tidal volume being established easing the mask to fit snugly on the bed of putty. Once the respiratory pattern appeared stable recording was started and a brief early expiratory airway occlusion was performed to check for air leaks around the mask. Recording was stopped and the pressure and volume traces checked for any signs of loss of volume from the closed system (when occluded) or loss of pressure. If there was any evidence of air leak (see Section 2.3) as evidenced by EEL step up, or fall of P during occlusion, the mask seal was checked and if necessary the mask reapplied.

With an established seal and the infant sleeping quietly, brief occlusions were performed during the expiratory portion of 20–25 breaths. Between each occlusion at least 6 breaths (usually 10) were allowed to monitor the state of the end expiratory level and to minimise the disturbance to the child's respiratory pattern. Occlusions were held for between 0.5 and 1 second, being released once:-

1. a pressure plateau had been established for at least 0.2 second,
2. after 1 second if no plateau was reached, or
3. inspiratory effort was evident on the P trace.

The occlusions were timed using the volume trace on the Tektronix oscilloscope, the aim being to achieve an even distribution of occlusions throughout the first 3/4 of expiration. Occlusions at lower volumes were attempted but if these disturbed the infant or repeatedly showed a failure of relaxation, they were abandoned as unlikely to prove successful and more prone to disturbing the baby than the higher volume occlusions.

Airway pressure, flow and volume were recorded continually during measurements, recording being temporarily stopped if the mask was removed. Studies on sedated infants were brought to a close once:-

1. adequate occlusions over a wide enough range of volumes and pressures had been collected for successful analysis, as judged from the oscilloscope,
2. the baby aroused and would not resettle,
3. IM atropine was given (infants measured pre operatively), or
4. if the baby continually failed to relax or to tolerate the facemask.
Frequent attempts at placing the mask were common, and some measurements are the result of a few occlusions performed between several mask replacements. The mask was removed immediately an infant aroused or showed signs of not tolerating the equipment. This limited data collection in 3 infants who were all receiving supplemented O\textsubscript{2} at the time of the measurements and whose O\textsubscript{2} saturation remained above 92% throughout the procedure.

**Anaesthetised infants**

In all infants measured during anaesthesia, this was induced with cyclopropane in O\textsubscript{2} (FiO\textsubscript{2} 0.5) and maintained with halothane 1-1.5 % in O\textsubscript{2} and N\textsubscript{2}O, FiO\textsubscript{2} 0.5. Following induction, suxamethonium IV 1 mg.kg\textsuperscript{-1} was given prior to intubation with a well fitting uncuffed red rubber or portex blue line tracheal tube, except for infants 61 and 71 who were intubated without muscle relaxant. The fit of the tube was gauged by the anaesthetist to give a high positive pressure leak for safety but minimal low pressure air escape. Once the tracheal tube was secured, several large inflations to pressures of 2.5 to 3 kPa were given to counter the effects of apnoea during intubation. When spontaneous ventilation was established, the measuring system was attached to the tracheal tube with an appropriate connector and the anaesthetic gas supplied to the T-piece. Checking that tidal volume and respiratory frequency were stable (unchanging from breath to breath, as displayed on the Tektronix 'scope) recording was started and a test occlusion was performed during early expiration to check for air leaks around the tracheal tube. This was assessed by listening for air loss around the tube during occlusion and checking the time based recording of the pressure and volume signals, see Section 2.4.

If there was evidence of a slight air leak around the tube, gentle cricoid pressure was applied to obliterate the leak as assessed by a repeat test occlusion. Once occlusions showed no evidence of leak on first inspection, Crs was measured as during sedated sleep, again making 20 to 25 brief airway occlusions. Measurements during spontaneous breathing were discontinued once:-

1. an adequate range of relaxed occlusions were believed to have been recorded,
2. there was evidence that the infant would not relax during any occlusions and thus the measurements should be abandoned, or
3. available time pre surgery had expired - an active policy of not intruding into theatre time being pursued in the interests of the child and to maintain good relations with the theatre and surgical personnel. If not completed before the measurements, calibration signals were recorded immediately the patient entered theatre, time permitting prior to the following patient's arrival in the anaesthetic room.

Paralysed anaesthetised infants

Paralysis

Measurements during neuromuscular blockade (resulting in total neuromuscular relaxation) were achieved in 6 infants (infant number 17, 39, 45, 15, 23, and 41) following administration of suxamethonium to facilitate tracheal intubation. In all other measurements on paralysed infants, paralysis was required for surgical purposes. Atracurium 0.5 mg.kg⁻¹ or d-tubocurarine 0.4 mg.kg⁻¹ was given intravenously once measurements during spontaneous breathing were completed.

Ventilation

During all paralysed measurements, ventilation was performed manually using the anaesthetic reservoir bag attached to the breathing system. In this size patient it is common practice to maintain a degree of positive end expiratory pressure (PEEP) by controlling the outlet of gas from the distal end of the anaesthetic bag. Since PEEP influences both lung volume and airway pressure measurements, this required considerable adaptation to the mode of ventilation.

From pilot studies it was established that the most reliable measure of gas volume above resting end expiratory level (EEL) present in the lungs during occlusions could be obtained from the amount of gas expired to resting EEL following release of the occlusion, see Fig 2.9.

To maintain adequate ventilation during measurements, airway occlusions were performed during every fifth passive expiration. The anaesthetist was asked to administer 5 inflations of suitable frequency and volume (as detailed in Section 3). The fifth inflation was followed by complete release of the end of the anaesthetic bag allowing a totally passive expiration, not influenced by PEEP. This expiration was occluded for ≈ 1 s, and on its release PEEP was avoided until the volume and airway pressure traces remained at a stable minimum for at least 1 s. A minimum of 5 occlusions were performed in this manner, encompassing the entire expiratory portion of
Figure 2.9a  Airway occlusion during paralysis, controlled ventilation. Flow zero during occlusion. Before reinflation there is at least 1 second during which end expiratory level remains constant and flow has returned to zero (note cardiac artifact on zero flow once shutter released). EEL fitted to stable V signal following deflation. Perpendicular O marks values for P and V used in analysis.

Figure 2.9b  Airway occlusion during spontaneous breathing. Zero flow during occlusion, airway pressure stable for > 0.2 s plateau. V returns to previous EEL. Perpendicular O marks values for P and V used in analysis.
the breath.
Ventilation was modified according to the study design as detailed in the following section, maintaining the principle of occluding every fifth expiration. Where time permitted, more than 5 acceptable occlusions were performed in any one mode of ventilation. This was taken as the absolute minimum acceptable when time was short.
Once measurements were completed, the child was reconnected to the standard anaesthetic breathing system and transferred to theatre. Since no response to stimulation was possible during paralysis, peripheral venous access could be established while measurements were in progress and any lower limb preparations completed.
Any calibration signals not recorded prior to the measurements were recorded at this stage.
Clinical measurements

All measurements on infants with respiratory disease were undertaken at Consultant clinicians' request. Where possible the infant's own respiratory efforts were measured (i.e. spontaneous breathing), depending upon the reasons for assisted ventilation if this was being applied.

Ventilated patients

When continuous positive pressure ventilation was required, the principles of measurement were the same as applied during paralysis. In this situation, however, if not paralysed for clinical purposes sedation with triclofos sodium via nasogastric tube was given to patients known to be disturbed by changes to ventilation. This served to both reduce any distress the patient may experience and increase the likelihood of obtaining informative measurements. Manual ventilation was given using the lowest pressures which maintained the child in a stable and settled state, as indicated by continuous transcutaneous PO$_2$ or pulse oximeter monitoring and behaviour. FiO$_2$ was maintained at the level being administered immediately prior to the measurements. Problems associated with leaks around tracheal or tracheostomy tubes were more common in this group of infants due to the long term nature of their tracheal intubation and heightened sensitivity to any airway interference such as gentle cricoid pressure.

Non-intubated patients breathing spontaneously

This group of infants were measured using the same protocol as for non-clinical sedated infants, with some minor adaptations. In cases where increased FiO$_2$ was necessary, the measurement system was used as for anaesthetised, spontaneous breathing measurements, supplying the O$_2$ and air mix to the anaesthetic T-piece with the reservoir bag unpressurised. Since by definition this group had more unstable respiratory status and pattern, there was an increased tendency for occlusions to disturb the child. These infants therefore often required longer than 10 breaths between occlusions to allow restabilisation and prevent respiratory embarrassment. These measurements were abandoned if air leaks could not be overcome, if airway occlusions persistently disturbed the patient, or if there was an unremitting failure to relax during airway occlusion. Following completion of a successful measurement, known signals were recorded using an appropriate inspired O$_2$ fraction, if this had not been completed previously.
Section 2.4

Analysis - Individual Data

Introduction
To ensure that Crs measurements were as accurate as possible, individual airway occlusions were only included in an analysis if they met certain acceptance criteria.

Acceptability of data
a) Flow signal.
Flow through the pneumotachograph was zero during an occlusion (no leak through the shutter, Fig 2.9).

b) Volume signal.
Spontaneous breathing
There should be at least 6 breaths between occlusions to enable the end expiratory baseline to be drawn or fitted accurately. Either a stable EEL, or one where the infant could be seen to be returning to the same EEL in a periodic fashion, was required for data to be included in analysis (Fig 2.10). Drift during occlusion was acceptable only if parallel to volume baseline. Sustained and progressive step-wise increase in EEL following occlusions indicated a leak around the mask or tracheal tube and any such data was discarded. Pronounced drift due to a leak around the apparatus was excluded by examination of the P trace (Fig 2.11). A marked drift of the volume trace could be indistinguishable from the effects of a leak. A slowly decreasing P during airway occlusion, as shown, confirmed the presence of a leak, irrespective of any volume drift.

Manual ventilation.
Manual positive pressure ventilation, particularly when delivering larger tidal volumes, tended to create pressures of > 3 kPa (≈ 30 cmH2O). At such pressures there was commonly an air leak around the tracheal tube during inflation. During passive deflation, with the route of least flow resistance being through the measurement system, such leaks tended to be minimised or abolished completely with gentle cricoid pressure. Thus although inspiratory leaks were evident on the volume trace, examination of the P trace (see below) confirmed absence of leaks during occlusion and subsequent deflation (Fig 2.12). In the paralysed infant, volume at occlusion was always taken as the passively expired volume following release of the occlusion (Figs 2.9,2.12) thus avoiding the inclusion of any data influenced by a leak. Data were
Figure 2.10a Stable end expiratory level during anaesthesia, spontaneous breathing. Note maintained respiratory cycle time despite P plateau of > 0.2 seconds.

Figure 2.10b Unstable end expiratory level during sedated sleep. Periodic return to the same minimum a) indicates variability is not due to a leak, and b) allows all occlusions to be referred to the same end expiratory lung V, reducing scatter of V - P data.
Figure 2.11 Leak around the mask or tracheal tube during airway occlusion. Spontaneously breathing infant. P fails to equilibrate (no P plateau), V end expiratory level steps up following release of the occlusion, failing to return to pre occlusion level. Compare with Fig 2.10b, unstable EEL.

Figure 2.12 Inspiratory leak around tracheal tube in a paralysed infant (controlled ventilation). Inspiratory V is apparently greater than expiratory, indicating loss of V from the apparatus/lung system. During occlusion P remains constant - leak not affecting expiration. δP and δV measured towards the end of the occlusion (at perpendicular O), see text.
accepted for analysis only if the end expiratory volume was constant, and zero flow attained, for at least one second prior to the next inflation (Fig 2.9).

c) Airway Opening Pressure (Tracheal/Mask).
During occlusion, a rapid rise to a plateau lasting at least 0.1 second was considered acceptable. During sedated sleep and when anaesthetised and paralysed, P plateau was frequently of the order of 0.5 to 1 second duration (i.e. pressure changing less than 0.02kPa, or 0.2 cmH₂O, during that time). Particularly during tracheal intubation, cardiac artifact was very prominent on the P trace (Fig 2.13). During high tidal volume ventilation, early expiratory occlusion occasionally resulted in a P which initially peaked and then decreased. Subsequent minimal change over 0.2 seconds indicated a minimising of the leak present at the start of the occlusion. When P stabilised in this way it was considered acceptable for inclusion in analysis (Fig 2.14).

Not accepted for analysis were occlusions during spontaneous breathing when there was either a slow rise in P with no plateau occurring (Fig 2.16), or a rise in P followed by a decrease (Fig 2.11). Both these may result from a leak around the mask or tube, or through the shutter (preventing equilibration of pressures). A rising P may indicate expiratory effort, invalidating the measurements. During manual ventilation, occlusions where there was no indication of P stabilising to an equilibrated plateau were discarded (Fig 2.15).

Manual analysis

Measurements during spontaneous breathing

Volume Identifying end expiratory points of the volume trace, a baseline was drawn in over as long a portion as possible. This was usually limited by volume being reset and continuity of baseline being lost.

Pressure Zero P was identified by dropping perpendiculars through points of zero flow during tidal breathing, to intersect the P trace. From this a P baseline was drawn.

Occlusion A perpendicular (true to the time base, not any drift effect on EEL) was drawn through the occluded volume and volume baseline at the point on the P trace considered to be the most representative of a plateau (Fig 2.9).

δV, occluded volume, was the perpendicular volume between the baseline and
Figure 2.13 Cardiac artifact on P trace, early reinflation following occlusion in intubated, paralysed infant. $\delta P$ plateau level determined as cardiac artifact minima (see text). Premature reinflation following occlusion has prevented V from reaching a stable constant level. $\delta V$ cannot be related to the same end expiratory lung V as prior occlusions. Evidence of PEEP between occlusions. Occlusion excluded from analysis.

Figure 2.14 High P leak during airway occlusion, paralysed infant receiving controlled ventilation. By the second half of the occlusion, P remains constant, indicating leak no longer present. $\delta P$ measured during this period is appropriate for the subsequent passively exhaled V.
Figure 2.15  Persistent leak during airway occlusion, paralysed infant. Since airway $P$ has not equilibrated during the occlusion, $\delta P$ cannot be measured. Occlusion excluded from analysis.

Figure 2.16  Failure of $P$ to equilibrate during occlusion, spontaneously breathing infant. Major cause of failure to obtain $Crs$ measurements from anaesthetised infants. Persistent increase in $P$ suggests expiratory muscle activity.
the volume trace (a constant value throughout the occlusion). 
\( \delta P \), plateau pressure was the perpendicular distance between the baseline and plateau. Where there was considerable cardiac artifact on the P plateau, a representative minimum was determined and this taken as the plateau level (see Fig 2.13).

**Measurements on paralysed infants**

**Volume.**
The volume baseline was drawn in to be consistent with the period of unchanging end expiratory level after full passive deflation following release of the occlusion (Fig 2.12). Any drift in volume during occlusion (providing this was not due to a leak through the pneumotachograph) was mirrored in the applied baseline.

**Pressure**
Following release of the occlusion any positive pressure within the breathing system was always released and during the period of unchanging volume baseline there was a corresponding period of zero (atmospheric) airway pressure. This was verified with the zero P recorded pre and post measurement, and if consistent taken as true zero, i.e. no PEEP. Any indication of the presence of PEEP implies that full deflation to passive FRC could not have occurred, thus the volume:pressure ratio determined from the two would have been inaccurate. The P baseline similarly was back extrapolated from the post occlusion recording. To minimise any error due to leak during occlusion (see above), a perpendicular (true to time) was dropped to measure \( \delta V \) and \( \delta P \) just prior to release of the shutter, rather than the initial period of the occlusion (Fig 2.12). \( \delta V \) was the perpendicular distance from baseline to occluded volume, \( \delta P \) the distance from the baseline to the pre-determined plateau point.

**All infants**
From the known signals recorded at the beginning or end of the measured trace (see Section 2.2) calibration factors for volume and airway pressure were calculated according to the formula:

\[
\text{CF} = \frac{\text{signal given (ml or cmH}_2\text{O)}}{\text{signal recorded on paper (cm)}}
\]

where CF = calibration factor; signal given = known signal (either 20 or 100 ml, 20 cmH\(_2\)O)

A. All occlusions, where there was no evidence of a leak or active respiratory effort during the occlusion, were analysed. If there were fewer
than 5 such acceptable occlusions, the measurement was deemed to have failed and no further analysis performed on that set of data other than record the reason for failure.

B. All accepted data pairs (occluded volume and plateau airway pressure) were then multiplied by the calibration factor. Data encompassing a pressure range of ≥ 3 cmH₂O (0.3 kPa) was considered acceptable.

C. All calibrated data were plotted as shown in Fig 1.3, and the slope of the regression line of volume (δV) on airway opening pressure (δP) obtained by least squares linear regression of the data. This was achieved either by entering the data into the statistical package ABSTAT⁵, or by using the linear regression facility on an hand held calculator.

Since \[ Crs = \frac{\delta V}{\delta P} \]

\[ \delta V = Crs \times \delta P + c \]

which is of the form \[ \delta V = b \delta P + c \]

Where \( b \) (Crs) is the slope of the regression line (regression coefficient) and \( c \) the constant term (intercept of the volume axis at zero pressure).

The reported value of Crs was that obtained by linear regression. This takes into account the potential effect of the infant breathing at a dynamically elevated FRC (Section 5.1, Olinsky 1976, Kosch 1984, Bryan 1984).

When analysing data from paralysed infants there should of course be no active elevation of end expiratory level, since all muscle activity was abolished and care was taken to allow time for full passive deflation. However, all data were reported using the same statistical methods to justify between state comparisons.

The correlation coefficient (R) for all regression lines was calculated as an indication of the closeness of association between the two variables V and P. Since there is a known close (linear) relationship, the value of R should be close to 1 in all cases. The square of the correlation coefficient measures the fraction of the total sum of squares of \( y \) (i.e. \( \delta V \)) that is explained by the regression, i.e. \[ R^2 = \text{fraction of variance of volume explained by the regression.} \]

Data were accepted if \( R^2 \geq 0.9 \) for individual slopes.
The precision of the regression coefficient, in this case total compliance, is improved by widely spread values of x (or plateau pressure), i.e.

Estimated variance (Crs) = residual variance of V about regression line

\[
\frac{\sum (x - \bar{x})^2}{Sxx}
\]

or

\[
\frac{s^2}{Sxx}
\]

and

\[
SE (Crs) = \frac{s}{\sqrt{Sxx}}
\]

Where \( x = \delta P \), \( \bar{x} = \text{mean } \delta P \), SE = standard error.

From this the 95% confidence interval for the true value of the slope (Crs) is

\[
Crs \pm t(0.05, n-2) \frac{s}{\sqrt{Sxx}}
\]  

(Osborne 1986)

These were calculated for all data, both as an indication of the quality of the data (larger CI => less certainty of Crs) and for the purpose of assessing the probability that any real change in Crs could be said to have occurred between states of measurement, see below (Section 2.5).
Section 2.5

Analysis - comparison between states (sedated, anaesthetised and anaesthetised paralysed).

In order to standardise for growth and allow meaningful comparisons to be made between infants of widely differing ages, results reported in Section 3.1 were expressed as the ratio of Crs obtained during paralysis to that recorded during spontaneous breathing (CrsP:CrsA) in each infant. The 95% CI for this ratio was also calculated for each infant (the width of the interval reflecting the scatter of volume data around the regression lines, the number of satisfactory occlusions obtained in each child, and the pressure range over which they were collected). The wider the CI, the larger the change that had to occur between any two states before the difference would be statistically significant (Bulpitt 1987, Altman 1988).

The data reported in Section 3.1 demonstrated no clear relationship between CrsA and CrsP, thus CrsP:CrsA for each infant was examined in detail to study the significance of individual differences.

In subsequent protocols there were far more significant changes both in individual and group data, permitting the use of a less cumbersome form of comparison between these data. Subsequent comparisons use the 95% CI for the actual regression lines obtained for each set of data. When comparing values of Crs from different states in individual children, this CI demonstrated clearly the probability of any difference between the states being due to chance (Bulpitt 1987, Altman 1988, Gardner 1988). Non-overlapping CIs indicate a statistically significant difference (p<0.05) between the slopes. Group data were compared using the Student's paired t-test. In order to standardise for the effects of growth and allow meaningful comparison to be made between children, values for Crs were also expressed as a percentage of the baseline value obtained during the initial measurement (when breathing spontaneously during either sedated sleep or anaesthesia).

Problems During Analysis

Analysis of Traces

Volume.

The most commonly encountered problem was that of an unstable end expiratory level, as shown in Fig 2.10. With continuous traces covering several occlusions it was possible to assess whether instability was in fact due to a leak (Fig 2.11) or true variability (Fig 2.10). This problem was
never present during anaesthesia, EEL being remarkable for its consistency (Fig 2.10). In only one anaesthetised infant, in whom tidal volume varied with time (Infant number 64), was there any instability of tidal ventilation during spontaneous breathing. In 3 sedated infants instability of EEL resulted in an unacceptable scatter of V-P data such that linear regression was inappropriate and the data excluded from the study (Infants 34,35 and 75). During measurements on paralysed infants, the anaesthetist was asked to release all pressure on the breathing system following release of the occlusion and delay the start of the subsequent inflation until no volume change had occurred for one second. This slight deviation from normal practice (in which a low level of PEEP is maintained) took time to perfect. Infants 2,20, and 73 were found to have PEEP present throughout recordings which excluded their data from analysis (Fig 2.17). Too hasty reinflations frequently resulted in the loss of some occlusions from analysis, as was the case for infants 51 and 53 (Fig 2.13), but did not result in the loss of a measurement in any child. The latter two problems both improved considerably with time and practice.

Airway Pressure

The most common cause of measurement failure during spontaneous breathing whilst anaesthetised was failure to relax during airway occlusion (Fig 2.16). This could occasionally be improved by increasing the Halothane to 1.5% but was still solely responsible for the loss of measurements of CrsA in 12 infants in the preliminary study, 2 in the second and 6 in the third comparisons (Sections 3.1, 3.2 and 3.3 respectively). The combination of low tidal volume (approximately 60% sedated), rapid respiratory rate, and possible drug interaction with the chemical control of breathing resulted in a pattern which preserved respiratory cycle time even during occlusion (Fig 2.10). The second common cause for exclusion of data due to P irregularities was glottic braking during sedation, where the infant apparently closed his glottis before pressure equilibration had occurred during airway occlusion (Fig 2.18). In some infants this was followed by an apparent equilibration period before the release of the occlusion (as indicated by a rise then stable plateau in P pressure). In these cases, where there was apparent absence of expiratory activity the data could be incorporated into the measurement analysis. Not infrequently the disturbance to the P equilibration could not be seen to stabilise and these data were lost.
Figure 2.17  Persistent PEEP during controlled ventilation. Incomplete release of the anaesthetic reservoir bag on release of occlusion prevents P from falling rapidly to atmospheric. Slight P reapplied before V end expiratory level can be established. Note effect of PEEP on elevating lung V; expiratory V following release of occlusion is considerably greater than inspiratory V.

Figure 2.18  Failure of P equilibration during occlusion possibly due to glottic activity. P appears to equilibrate but then increases to a second apparent plateau. Occlusion excluded from analysis.
Problems of Leak
These have been discussed in detail elsewhere (equipment specifications and development, acceptability of data, this section). In summary, a large number of early measurements were lost due to poor reliability of the shutter mechanism. This was clearly identified on most traces as the fall in P pressure (or absence of a plateau) during occlusion, accompanied by a fluctuation on the flow signal and thus a real change in volume during the occlusion. Leak around the face mask was usually spotted within one or two occlusions as a failure of P to plateau and sequential stepping up of the volume trace (Fig 2.11). This was corrected immediately it was detected. However, one measurement on a sedated infant was lost due to a persistent small leak present throughout the measurement but not obvious during data collection. Leaks around the tracheal tube, as mentioned earlier, were abolished using gentle cricoid pressure. Leaks during high volume inflations (and therefore higher inflation pressures) did not necessarily exclude data from inclusion, as mentioned earlier (acceptability of data).

Time and Patient related problems.
One problem over which there was little control was the small child fasted for surgery who failed to sleep, despite otherwise adequate sedation (4 infants). There were also occasions where pressure of time in the anaesthetic room resulted in less (quantitatively) data being collected, and also when theatre considerations resulted in the loss of sequential measurements during anaesthesia.

Conclusion
Despite the loss of data due to technical problems (leak through the shutter), failure of the infant to relax, and inappropriate manual ventilation (PEEP), most data could be analysed to a common standard. With experience, very few measurements were lost due to poor quality of the data, allowing between-state comparisons in almost all infants examined.
Section 2 Summary

1 The equipment used in this study was assessed for the ability to record faithfully the events under investigation, and where possible was designed to minimise the influence of the equipment on the parameters under investigation. Calibration signals of known magnitude were recorded during every measurement session.

2 The single measurement system was designed to be easily adapted for use with infants breathing spontaneously through a face mask or tracheal tube, or with infants receiving controlled ventilation (through a tracheal tube).

3 Potential problems of data collection could be identified by inspecting the time based recordings of each study. Thus data was only accepted if any influence of a leak could be discounted, and there was no evidence of failure of equilibration of airway/alveolar pressure during occlusion.

4 To allow for any active elevation of EEL (and in the case of data collected during paralysis, for consistency of data handling), least squares linear regression analysis was used to obtain the slope of the volume-pressure data, and thus Crs.

Two statistical approaches were used to examine the data. In the first comparison (Section 3.1), the 95% CI for the difference between slopes in a particular infant was calculated to indicate the probability of a real change in Crs having occurred between measurements. In Sections 3.2 and 3.3, a more straightforward approach was used. The 95% CIs for the slopes themselves were compared to indicate whether changes in Crs were significant, or likely to be due to chance.
Section 3

Application of the Multiple Occlusion Technique

Introduction
This section describes the application of the MOT to measure Crs in sedated, anaesthetised and anaesthetised paralysed infants. The effects of anaesthesia and of pattern of ventilation on Crs measurements were largely unknown in infants and young children primarily due to the lack of a single suitable technique which could be applied to this age group. The multiple occlusion technique (MOT) for measuring Crs had been applied successfully to spontaneously breathing neonates, including those receiving assisted ventilation (Thomson 1985, 1983). The technique had not been applied to anaesthetised infants, yet could potentially be used to measure Crs in the same infant under any state of consciousness, both during spontaneous breathing and when receiving manual ventilation.

Section 3.1 describes an initial exploratory study in which the feasibility of measurements in the operating suite was assessed. The results of the preliminary comparison between Crs during spontaneous breathing with that during paralysis and manual ventilation are reported. These early measurements prompted a closer examination of the effects of manipulating the pattern of ventilation on the resulting values of Crs.

Section 3.2 describes the effect on Crs of changing tidal volume during manual ventilation of the paralysed infant. Having studied the influence of mode and pattern of ventilation on Crs, the effects of anaesthesia per se were examined.

Section 3.3 examines the influence of the induction of anaesthesia on Crs in infants and young children aged from 1 to 25 months.

The interpretation of the findings in Sections 3.1 to 3.3 are discussed more fully in Section 5.
Section 3.1

Crs during anaesthesia - a preliminary study.

Measurements for Crs obtained in anaesthetised children and infants have been quoted as reference values for non-anaesthetised patients. Such values were frequently obtained using methods inappropriate for the latter group. The MOT had already been applied successfully to spontaneously breathing neonates, and potentially could be applied to those receiving assisted ventilation. Successful measurements of Crs by the MOT depend upon total respiratory muscle relaxation during brief airway occlusion in expiration, by evoking the Hering Breuer inflation reflex in the spontaneously breathing infant. In the absence of such relaxation the technique is invalid. If, however, such relaxation is achieved, then repeat measurements in the same infant when paralysed and receiving manual ventilation should closely match those obtained before paralysis. Thus the results should be interchangeable and the MOT a means of monitoring Crs in the ventilated infant, using the same technique, both during intermittent positive pressure ventilation (IPPV) and during recovery when breathing spontaneously, whether intubated or not.

The aims of this preliminary study were to:
1. Assess the practicalities of using the MOT in anaesthetised infants and measure Crs during spontaneous breathing in these infants. No such data were available at the time of the study.
2. To test the hypothesis that measurements of Crs in the paralysed ventilated infant are the same as those during spontaneous breathing, by using the MOT and performing paired measurements of Crs in a group of anaesthetised infants.

Subjects
All infants and young children under 3 years of age receiving general anaesthesia with tracheal intubation and neuromuscular relaxation (paralysis) were considered for inclusion. To minimise any influence of pathology on the results, those with overt respiratory disease were excluded from the study. 46 infants were recruited, whose personal details appear in table 3.9.
Methods

Pre-medication was given according to the established hospital practice. Infants weighing less than 10 kg received Pethidine compound 0.08 ml.kg\(^{-1}\) (1 ml contains Pethidine 25 mg, promethazine 6.25 mg, and chlorpromazine 6.25 mg) given with atropine 0.02-0.08 mg.kg\(^{-1}\) 1 hour pre operatively. Those weighing ≥ 10 kg were pre medicated with papaveretum 0.4 mg.kg\(^{-1}\) and hyoscine 0.008 mg.kg\(^{-1}\).

Three infants in whom Crs was to be measured pre operatively, infants number 34, 35 and 44, were pre - medicated with triclofos sodium, 100 mg.kg\(^{-1}\) orally (see Section 3.3), and atropine as above.

Induction of anaesthesia, tracheal intubation and Crs measurements were completed as described in Section 2. Before measurements during paralysis were made, (CrsP), each infant was given a lung volume history by inflating the lungs to a pressure of 2.5 to 3 kPa for 3 successive breaths. No attempt was made to control the pattern of ventilation given by the anaesthetist to the paralysed infant subsequent to the volume history, except during the expiration following release of an airway occlusion. During these passive expirations, adequate time was allowed for the lung to reach its relaxed, passively determined, resting volume prior to the next inflation.

At the completion of Crs measurements, the infant's length was recorded using an infant measuring rod (Secca). Also recorded were the infant's date of birth, weight as recorded prior to anaesthesia, and any relevant past medical history (this having been reviewed prior to accepting the infant for inclusion in the study).

Statistical analysis

See Section 2.4. All values for Crs reported here were calculated by least squares regression analysis of the V - P data obtained from multiple expiratory occlusions.

The ratio of Crs during paralysis to Crs during spontaneous breathing (when anaesthetised), CrsP : CrsA, and the 95% confidence interval (CI) for this ratio was calculated for each infant, as were the 95% CIs for each V - P regression line.
Results

In 23 infants successful paired measurements of CrsA and CrsP were obtained.

In 19 infants a value for Crs was obtained in one or other state (CrsA or CrsP) but not in both. The results obtained for these patients and the reasons for failure are given in table 3.1.

During this preliminary study, data were lost or measurements had to be abandoned on 5 occasions due to leaks through the shutter mechanism (shutter design 1, see Section 2.1).

The values for Crs obtained from the 23 successful paired measurements are given in table 3.2, together with the 95% CIs for the individual V - P slopes, and the mean and 95% CI for the CrsP : CrsA ratio for each infant.

The variability of absolute values for CrsA obtained from individual infants largely reflects the rapid increase in Crs with growth which occurs during the first two years of life.

The 23 infants showed considerable variability in their response to paralysis and manual ventilation.

In some infants, CrsP was similar to CrsA, with similar 95% CIs for the slopes of the V - P data obtained under both conditions, and narrow CIs of the CrsP : CrsA ratios encompassing unity (e.g. infants 1, 19 and 23).

In such infants any difference between the two states was not statistically significant and was probably too small to be of clinical or physiological importance. Fig 3.1 illustrates the results from infant 1, in whom the values for Crs were virtually the same in both states.

In other infants, CrsP was also similar to CrsA, with the CrsP : CrsA ratio encompassing unity, but the 95% CIs for the ratio were so wide that it was difficult to conclude that no real difference existed despite high 'P' values (e.g. infants 4, 34 and 35). The results from infant 35 are illustrated in Fig 3.2

The remaining infants demonstrated an increase in Crs, following paralysis, with the whole of the 95% CI for the ratio being greater than unity (such as infants 33, 40 and 49). Even in infants with wider CIs (such as infants 10 and 33) the differences were so large that the increases were significant.

Results from infant 33 are shown in Fig 3.3.

All infants in whom there was no overlap of 95% CIs for the individual CrsA and CrsP values, showed significant increases in Crs during paralysis (p < 0.02).

There were no occasions on which CrsP was significantly lower than CrsA.
Figure 3.1 V - P data for infant number 1. CrsA and CrsP are similar, with similar 95% CIs.

Figure 3.2 V - P data for infant number 35. Although CrsA and CrsP are similar, a difference may exist between the two measurements.
Figure 3.3 V - P data for infant number 33. CrsA is significantly less than CrsP.
Table 3.1 Infants in whom Crs measurements failed in one or both states - preliminary study

<table>
<thead>
<tr>
<th>Infant number</th>
<th>CrsA</th>
<th>CrsP</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>FTR</td>
<td>100.7</td>
</tr>
<tr>
<td>7</td>
<td>FTR</td>
<td>78.2</td>
</tr>
<tr>
<td>9</td>
<td>FTR, SL</td>
<td>84.2</td>
</tr>
<tr>
<td>12</td>
<td>FTR</td>
<td>91.8</td>
</tr>
<tr>
<td>13</td>
<td>FTR</td>
<td>50.4</td>
</tr>
<tr>
<td>14</td>
<td>FTR</td>
<td>34.1</td>
</tr>
<tr>
<td>16</td>
<td>55.1</td>
<td>Scatter(alinear)</td>
</tr>
<tr>
<td>20</td>
<td>91.0</td>
<td>TL</td>
</tr>
<tr>
<td>21</td>
<td>FTR</td>
<td>43.9</td>
</tr>
<tr>
<td>24</td>
<td>25.6</td>
<td>SL</td>
</tr>
<tr>
<td>26</td>
<td>FTR</td>
<td>40.2</td>
</tr>
<tr>
<td>31</td>
<td>65.3</td>
<td>TL</td>
</tr>
<tr>
<td>36</td>
<td>FTR</td>
<td>31.6</td>
</tr>
<tr>
<td>39</td>
<td>FTR</td>
<td>114.1</td>
</tr>
<tr>
<td>41</td>
<td>No time</td>
<td>112.7</td>
</tr>
<tr>
<td>42</td>
<td>FTR</td>
<td>150.7</td>
</tr>
<tr>
<td>43</td>
<td>FTR, SL</td>
<td>104.9</td>
</tr>
<tr>
<td>45</td>
<td>No time</td>
<td>71.3</td>
</tr>
<tr>
<td>46</td>
<td>No time</td>
<td>40.7</td>
</tr>
<tr>
<td>2</td>
<td>FTR</td>
<td>TL, PEEP</td>
</tr>
<tr>
<td>18</td>
<td>SL</td>
<td>SL</td>
</tr>
<tr>
<td>38</td>
<td>FTR</td>
<td>Scatter(variable Vt)</td>
</tr>
<tr>
<td>47</td>
<td>No time</td>
<td>Technical failure</td>
</tr>
</tbody>
</table>

CrsA - Crs during anaesthesia, breathing spontaneously
CrsP - Crs during anaesthesia paralysis, manual ventilation
FTR - failed to relax during airway occlusion
SL - leak through shutter during occlusion
TL - leak around the tracheal tube
PEEP - positive end expiratory pressure
Scatter - marked scatter of V - P data
Table 3.2 Crs during anaesthesia and anaesthesia paralysis.
Preliminary study, anaesthetist - determined tidal volume

<table>
<thead>
<tr>
<th>Infant number</th>
<th>CrsA (ml.kPa⁻¹)</th>
<th>CrsA 95% CI</th>
<th>CrsP (ml.kPa⁻¹)</th>
<th>CrsP 95% CI</th>
<th>CrsP:CrsA ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96.2 (87.9 - 104.7)</td>
<td>103.8 (86.5 - 119.1)</td>
<td>1.08 (0.93 - 1.23)</td>
<td>0.275</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>138.7 (89.7 - 187.7)</td>
<td>123.8 (76.3 - 171.2)</td>
<td>0.89 (0.44 - 1.34)</td>
<td>0.619</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>131.6 (123.6 - 139.5)</td>
<td>150.8 (135.1 - 166.5)</td>
<td>1.15 (1.03 - 1.26)</td>
<td>0.014</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>82.7 (75.5 - 89.9)</td>
<td>96.6 (89.9 - 103.3)</td>
<td>1.17 (1.05 - 1.29)</td>
<td>0.009</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>79.5 (53.8 - 105.3)</td>
<td>112.0 (101.6 - 122.6)</td>
<td>1.41 (1.13 - 1.69)</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>89.3 (73.6 - 105.1)</td>
<td>94.2 (88.2 - 100.2)</td>
<td>1.05 (0.89 - 1.21)</td>
<td>0.156</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>41.5 (37.4 - 45.7)</td>
<td>48.6 (44.6 - 52.6)</td>
<td>1.17 (1.04 - 1.30)</td>
<td>0.015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>33.1 (30.0 - 36.6)</td>
<td>28.9 (23.2 - 34.6)</td>
<td>0.87 (0.69 - 1.05)</td>
<td>0.156</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>103.8 (91.6 - 116.0)</td>
<td>108.5 (97.1 - 119.8)</td>
<td>1.05 (0.89 - 1.20)</td>
<td>0.556</td>
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</tr>
<tr>
<td>23</td>
<td>131.7 (122.1 - 141.1)</td>
<td>135.9 (128.5 - 143.4)</td>
<td>1.03 (0.94 - 1.12)</td>
<td>0.463</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>37.1 (33.5 - 40.7)</td>
<td>44.9 (41.2 - 48.7)</td>
<td>1.21 (1.08 - 1.34)</td>
<td>0.015</td>
<td></td>
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<td>59.1 (53.2 - 65.0)</td>
<td>1.47 (1.26 - 1.68)</td>
<td>0.001</td>
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CrsA Crs during anaesthesia, breathing spontaneously
CrsP Crs during anaesthesia paralysis, manual ventilation.
95% CI = 95% confidence interval
p = p value for paired t-test between states

Taking the group as a whole, mean CrsP:CrsA was 1.17 (95%CI 1.06 - 1.28, p = 0.005 Student's paired t-test). This represents a mean increase in Crs of 9.74 ml.kPa⁻¹ during anaesthesia paralysis.

There was no evidence that CrsA:CrsP changed systematically with age (R² < 0.02 for CrsP:CrsA regressed against weight).
Discussion – specific implications.

The application of the MOT to measure Crs in anaesthetised spontaneously breathing infants.

The MOT had been successfully applied to measure Crs in anaesthetised intubated infants, proving more successful in paralysed infants receiving manual ventilation than in those breathing spontaneously. This difference was primarily due to the fact that values of Crs obtained during paralysis cannot be invalidated by active expiration.

Of 46 attempted measurements during paralysis, 38 successful measurements were obtained. 4 of the failures were due to technical problems (including shutter failure) which could potentially be overcome in future studies. The remainder were due to leaks around the tracheal tube, or excessive scatter of the V - P data. During spontaneous breathing the success rate was lower, with persistent failure to relax during occlusion being responsible for 12 of the 19 failed measurements, the remainder being attributable to leaks or shortage of time (table 3.1). The problems, including failure to relax during airway occlusion, of measuring Crs in the anaesthetised, spontaneously breathing infant are discussed more fully in Section 5.

Crs was successfully measured in both states, spontaneous breathing and paralysis, in 23 infants.

Despite the relatively high success rate of measurements made during paralysis, there was such excessive scatter of the V - P data in 2 infants (16 and 38), that linear regression analysis was not an appropriate form of analysis. Data from a third infant, infant 34, was also very scattered, but just fulfilled the acceptance criteria, with a squared correlation coefficient of 0.9.

Since expiratory effort was impossible and air leaks during occlusion had been excluded as source of error, this scatter had to have some underlying physiological or technical explanation.

One possible explanation was alinearity of the V - P data, which would have resulted in scatter of the V - P data around any linear regression line. This was indeed the case for infant 16, V - P data from the higher occluded volumes being visibly alinear with respect to lower volumes. In this instance the apparent alinearity made it impossible to calculate a single slope for the data, making any comparison between CrsA and CrsP impossible.

The scatter of data seen in the other 2 infants could not be so explained. The V - P data obtained for CrsP for infants 34 and 38 are illustrated in
Figure 3.4  Marked scatter of V - P data when paralysed (CrsP), infants number 34 and number 38.

Figure 3.5  Crs during paralysis (calculated as $\delta V \div \delta P$ from individual occlusions) plotted against time, infants number 34 and 38.
Providing adequate expiratory time was allowed with zero applied pressure, there were no mechanisms acting to elevate lung volume above passively determined resting lung volume in the paralysed infant. Thus Crs determined by dividing the equilibrated airway pressure during occlusion into the subsequently expired volume ($\Delta V \div \Delta P$), should have resulted in an accurate measure of Crs at that moment in time.

Crs was calculated in this manner for sequential occlusions for infants 34 and 38, and the resulting values plotted against elapsed time (Fig 3.5).

As can be seen from Fig 3.5, in both infants there appeared to be a time related progressive change in CrsP.

The increase in CrsP shown by infant 34, and the decrease by infant 38, were found to be accompanied by different patterns of manual ventilation during paralysis. From the time based recordings of tidal volume and airway pressure, infant 34 could be seen to be have received fairly vigorous manual ventilation of 60 breaths per minute with peak airway pressures of between 2.5 and 3.0 kPa. In contrast to this, infant 38 received exceptionally gentle ventilation with peak inspiratory pressures of 2.0 to 2.5 kPa at a rate of 15 breaths per minute. Within 4 minutes of such ventilation CrsP had halved.

**CrsA and CrsP as interchangeable measurements of Crs**

Results from this study have shown that values for Crs obtained from anaesthetised paralysed infants are not necessarily interchangeable with those obtained from the spontaneously breathing infant.

Of the 23 infants in whom paired measurements were successful, only a small number could be said to have interchangeable values for Crs. The remaining infants with similar values for CrsP and CrsA had such wide CIs for their CrsP : CrsA ratio, that there may have been a difference between the two values, but there were inadequate data to judge conclusively. Wide CIs for the CrsP : CrsA ratios are a reflection of the pressure range over which data were available, and the scatter and number of data points included, in each case. Minimising the width of the CIs increases the probability of reaching meaningful conclusions when comparing two measurements of Crs. This can be achieved by performing a large number of airway occlusions over as wide a pressure range as possible. All the data reported here met the inclusion criteria described in Section 2, encompassing a pressure range of 0.3 kPa, and $R^2 \geq 0.9$. This emphasises the need to obtain adequate data when attempting to compare Crs measurements within
an infant.

The possible dependence of CrsP on pattern of ventilation may have explained much of the variability in response to paralysis seen in this group of infants.

Lung volume is known to fall during halothane anaesthesia in adults, probably primarily due to compression atelectasis (Rehder 1985, Brismar 1985, Hedenstierna 1985a). The lung of reduced volume is less compliant than the normally inflated lung, greater pressures being required to increase lung volume by any given amount. Reduced ventilation may have resulted in progressive atelectasis and small airway collapse, effectively further decreasing Crs.

Conversely, the more aggressive ventilation received by infant 34, at a rate which may have inhibited full expiration to passively determined end expiratory lung volume between occlusions, may have facilitated progressive reinflation of any atelectic areas of the lung, normalising lung volume and thus improving Crs.

Although the MOT had been used successfully to measure both CrsA and CrsP, the differences between CrsA and CrsP were too variable between infants to be able to characterise the response to paralysis. This variability, and the pattern of changes over time seen in infants 34 and 38, suggested that close attention may need to be given to the pattern of ventilation during measurements.

Thus in conclusion, this preliminary study led to the hypothesis that although Crs could be measured during both spontaneous breathing (CrsA) and manual ventilation (when paralysed, CrsP) in the anaesthetised infant, the resulting values for CrsP may be influenced by the pattern of ventilation given at the time of measurement.
Section 3.2

The influence of tidal volume on Crs measurements

Introduction
From the results of the preliminary study described in Section 3.1, there appeared to be a relationship between tidal volume administered and Crs measured by the MOT in ventilated anaesthetised infants. Although such a potential influence has been referred to by several authors in the past (Nims 1955, Richards 1961, Egbert 1963, Gold 1965, Fisk 1970, Grimby 1975), any effect this may have on results obtained using the MOT had not been reported.

With the increasing use of the MOT to measure Crs in infants for clinical and research purposes, it was important to acquire a greater understanding of the influence such mechanisms may have on the results so obtained.

The aim of this study was to determine the potential influence of tidal volume on measured values of Crs using the MOT, by measuring Crs in anaesthetised intubated infants and young children both during spontaneous breathing (CrsA) and following paralysis when ventilated with both small and large tidal volumes.

Subjects
Infants and young children up to 2 years of age requiring anaesthesia and tracheal intubation for surgical purposes were considered for recruitment. Infants with cardio respiratory or musculoskeletal disease and those under 6 months postnatal age, if less than 36 weeks gestational age at birth, were excluded. Infants with renal disease were only included if there was no evidence of concomitant respiratory abnormality or disease.

Methods
Following induction of anaesthesia and tracheal intubation as described in Section 2, measurement of Crs was made once the infant was breathing spontaneously with regular tidal volume and frequency. This value for Crs (CrsA) served as a baseline reference for comparison with values obtained during paralysis. With the administration of the neuromuscular blocking agent following completion of CrsA measurement, the anaesthetist commenced manual ventilation mimicking the tidal volume and frequency displayed on the oscilloscope during spontaneous breathing. Once paralysis was complete, Crs
was measured maintaining this low volume ventilation as determined by the child prior to paralysis (CrsLV) (Section 2).

On completion of the low volume study, 3 to 5 large inflations to a pressure of 2.5 to 3 kPa (≈ 25 - 30 cmH₂O) were given. This ensured all infants commenced the subsequent high volume ventilation from a standard volume history, which mimicked conditions at the beginning of the study, when several large inflations had been administered prior to and following intubation (Section 2.2). Manual ventilation was then continued with tidal volumes approximately double those used during the low volume study, and Crs measurements repeated at this high tidal volume (CrsHV). To allow time for a stable end expiratory level to be achieved on release of the occlusions, respiratory frequency decreased with the increase in tidal volume.

In 2 infants there was adequate time prior to surgery for the LV measurements to be repeated after the HV study (CrsLV2).

**Results**

Infant details are given in table 3.9.

Of the 22 anaesthetised infants and young children included in the study, 2 (infants 70 and 74) failed to relax during occlusions when spontaneously breathing (CrsA measurement).

In 20 infants, Crs was successfully measured in all 3 ventilatory states, giving CrsA, CrsLV and CrsHV. In 2 of these, infants 61 and 62, CrsLV2 was also measured.

The respiratory parameters of frequency and tidal volume during the 3 ventilatory states for each infant are given in table 3.3. Table 3.4 gives the individual values of Crs and their 95% CI for each state in each infant.

The V - P data obtained for infant 68 in the 3 ventilatory states are shown in Fig 3.6.

During low volume ventilation there was a mean increase in Crs of 6.6% when compared with values obtained during spontaneous breathing (CrsA, range -26% to +45%). In all but 3 infants (56,63, and 79), these changes were not significant at the < 5% level, as shown by the overlap of the 95% CIs.

When tidal volume was increased, Crs increased significantly in all infants with respect to CrsA, as illustrated by the clear separation of the 95% CIs for these 2 parameters. For the group results, a highly significant increase in Crs occurred with the increase in tidal volume (p < 0.0001). This increase, from CrsLV to CrsHV, was also significant at the < 5% level for
Figure 3.6 V - P data for infant number 68. CrsA and CrsLV significantly less than CrsHV.

Figure 3.7 Change in Crs during low- and high-volume ventilation for all 20 infants. Results expressed with respect to values obtained from the same infant during spontaneous breathing. Low vol = low volume ventilation, High vol = high volume ventilation.
Figure 3.8a  Relationship between changes in Crs and changes in tidal volume (Vt) after paralysis. Expressed as percent change from values obtained during spontaneous breathing.

Figure 3.8b  Relationship between changes in Crs (δCrs) and changes in tidal volume (δVt) after paralysis. Expressed as absolute changes from values obtained during anaesthesia, spontaneously breathing, per kg body weight. Regression line $\delta$CrsHV (ml.kPa$^{-1}$.kg) = 0.89851 + 0.550895Vt (ml.kg$^{-1}$) ($R^2$ = 0.68) is shown.
all individuals but infant 54. Fig 3.7 summarises the changes in Crs with the large and significant increase during HV ventilation and small mean change but wide scatter during LV ventilation.

Exact matching of tidal volumes and frequencies during manual ventilation to those observed during spontaneous breathing was difficult to achieve, particularly when respiratory rates were as rapid as 80 breaths per minute. Although tidal volume was well matched in some infants (51, 62, and 78 for example), in others there were considerable differences between the two states (infants 52, 54, and 61). Fig 3.8a illustrates the relationship between % increase in Crs and % increase in tidal volume, with respect to spontaneous breathing values ($R^2 = 0.58$, $p < 0.001$). This relationship was stronger still when absolute changes in Crs and $V_t$ were corrected for body weight, as shown in Fig 3.8b ($R^2 = 0.68$ for CrsHV). Such a relationship was not present between changes in frequency and changes in Crs ($R^2 = 0.01$, $p > 0.1$).

In the two infants in whom repeat measurements of CrsLV were made, the fall to values approaching those obtained prior to CrsHV measurement was immediate and significant in each case.

<table>
<thead>
<tr>
<th>Crs in ml.kPa$^{-1}$ (95% CIs in brackets)</th>
<th>Infant 61</th>
<th>Infant 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrsLV</td>
<td>60.2 (56.3 - 64.1)</td>
<td>56.4 (51.2 - 61.6)</td>
</tr>
<tr>
<td>CrsHV</td>
<td>95.5 (87.8 - 103.1)</td>
<td>94.6 (90.6 - 98.5)</td>
</tr>
<tr>
<td>CrsLV2</td>
<td>59.4 (52.3 - 66.6)</td>
<td>61.6 (59.4 - 63.8)</td>
</tr>
</tbody>
</table>

All values for Crs quoted here were derived from least squares linear regression analysis of the individual's $V - P$ data, with squared correlation coefficients ($R^2$) of between 0.93 and 0.99 (all but 7 of 62 plots having an $R^2 > 0.97$). There was some evidence of alinearity of the $V - P$ data in the high volume plots of infants 57, 60 and 62, despite $R^2$ values in excess of 0.985. Fitting a first order polynomial ($V = k + aP + bP^2$), the factor describing the curvilinearity (the $P^2$ term) was more than twice as great as its standard error, i.e. $b > 2SE(b)$, suggesting a statistically significant improved fit compared with linear regression. In these infants a significant increase in Crs occurred whether results were obtained from mean volume to pressure ratios or linear regression analysis.

In no instance was there evidence of curvilinearity in LV ventilation measurements of CrsLV.
Reproducibility of measurements
Duplicate measurements of Crs for assessing reproducibility were possible in
1 anaesthetised infant during spontaneous breathing and 3 during anaesthesia
paralysis (while maintaining the same tidal volume and respiratory rate).
The difference between paired measurements in these 4 infants varied from
-4.9% to 4.7% (mean -1.3%).

Table 3.3 Tidal volume and Respiratory frequency during anaesthesia and
anaesthesia paralysis with low and high tidal volume ventilation

<table>
<thead>
<tr>
<th>Infant number</th>
<th>Vt</th>
<th>f</th>
<th>Vt</th>
<th>f</th>
<th>Vt</th>
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Vt tidal volume
f respiratory frequency (bpm = breaths per minute)
Crs as in table 3.4
Table 3.4 Crs during anaesthesia, and anaesthesia paralysis with low and high tidal volume ventilation (95% confidence intervals in parentheses)

<table>
<thead>
<tr>
<th>Infant number</th>
<th>CrsA (CrsA 95% CI) ml.kPa⁻¹</th>
<th>CrsLV (CrsLV 95% CI) ml.kPa⁻¹</th>
<th>CrsHV (CrsHV 95% CI) ml.kPa⁻¹</th>
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</thead>
<tbody>
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<td>60.0 (57.7 - 62.2)</td>
<td>64.9 (60.8 - 68.9)</td>
<td>76.3 (70.6 - 82.0)</td>
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<tr>
<td>52</td>
<td>45.9 (40.9 - 50.9)</td>
<td>51.4 (48.5 - 54.4)</td>
<td>96.0 (79.0 - 112.9)</td>
</tr>
<tr>
<td>53</td>
<td>67.7 (55.6 - 79.7)</td>
<td>67.4 (63.1 - 71.7)</td>
<td>108.8 (83.5 - 134.0)</td>
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<td>54</td>
<td>61.4 (57.9 - 65.0)</td>
<td>72.9 (63.7 - 82.1)</td>
<td>90.4 (76.3 - 104.6)</td>
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<td>21.8 (20.2 - 23.4)</td>
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<td>57</td>
<td>104.9 (98.0 - 112.5)</td>
<td>123.2 (109.1 - 137.5)</td>
<td>166.1 (154.6 - 177.5)</td>
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<td>30.6 (26.2 - 35.0)</td>
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<td>50.3 (46.4 - 54.2)</td>
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<tr>
<td>60</td>
<td>70.6 (62.2 - 78.8)</td>
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<td>87.8 (82.0 - 93.6)</td>
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<td>199.5 (178.2 - 220.8)</td>
</tr>
<tr>
<td>79</td>
<td>16.3 (13.3 - 19.2)</td>
<td>22.0 (21.1 - 22.9)</td>
<td>42.1 (39.3 - 44.8)</td>
</tr>
</tbody>
</table>

CrsA  Crs when anaesthetised, breathing spontaneously
CrsLV Crs when anaesthetised and paralysed, tidal volume ≈ that during CrsA measurement
CrsHV Crs when anaesthetised and paralysed, tidal volume ≈ 2x that during CrsA measurement
CI   confidence interval
Discussion - specific implications.

Crs measured by the MOT yielded values which could be altered by manipulating tidal volume in the anaesthetised, paralysed, infant and young child. Increasing tidal volume resulted in a significant increase in Crs compared with that measured when the infant was permitted to breathe spontaneously or was ventilated manually with a similar tidal volume and frequency to that during spontaneous breathing.

This increase in Crs occurred in all infants, with a direct relationship being apparent between increase in tidal volume and corresponding increase in Crs, particularly when these were corrected for the infant's body weight. Ventilating with larger tidal volumes resulted in apparent ailinearity of the V - P data of the respiratory system in some infants. The increase in Crs appeared to be short lived, its persistence being dependent upon a maintained high volume ventilation in the paralysed infant. This suggested that the large inflations given prior to the HV measurements had limited influence on the results, particularly the difference between spontaneous breathing and CrsHV. The rapid reversibility of the increase in Crs during HV ventilation with changing ventilation also implied that the changes in Crs were due mainly to the pressure volume characteristics of the lung and chest wall rather than to mechanisms which were time - dependent, such as the absorption of gases, or changes in pulmonary or thoracic blood flow.

These results are from anaesthetised individuals believed to be of normal respiratory status. They cannot therefore be extrapolated directly to the non anaesthetised infant with respiratory disease. It is conceivable, however, that measurements of Crs in the latter may also be dependent upon the precise ventilatory parameters applicable at the time of measurements. Having verified that tidal volume directly influenced values obtained for Crs in the anaesthetised paralysed infant, this had implications when comparing Crs during anaesthesia with Crs measured during the non anaesthetised state. Although values obtained in anaesthetised infants have been quoted in the past as reference values for non anaesthetised infants, the fact that such values were obtained from paralysed, anaesthetised infants makes this practice inappropriate.
Having ascertained that the pattern of ventilation did indeed influence Crs measurements in the anaesthetised infant, the influence of anaesthesia on Crs remained unclear.

To improve understanding both of the role of anaesthesia itself in determining Crs, and the relevance of the relationship between ventilation and measured values for Crs, it would be necessary to perform measurements both pre and post induction of anaesthesia in the same infant. In light of the reduction in absolute lung volume and tidal volume reported in both adults and infants when anaesthetised, Crs may be expected to be similarly reduced compared to pre induction values.
Section 3.3

The influence of halothane anaesthesia on Crs

In the study reported in section 3.2, Crs values obtained using the MOT in the anaesthetised paralysed infant were shown to be influenced by the tidal volume at the time of measurement.

It was clear that comparisons between values for Crs obtained in different ventilatory states - spontaneous breathing, and manual ventilation, may well reflect the mode of ventilation during measurements as much as any change in Crs due to other physiological factors such as altered lung perfusion. For longitudinal monitoring of patients receiving ventilatory support, any changes in Crs may need to be interpreted taking full account of any concurrent changes in ventilation. Since the desired information is usually an indication of the infant's status at the time of measurement, comparisons over time are not inappropriate.

However, in the anaesthetised infant, the effect of anaesthesia on Crs cannot be determined by pooling data from different states, or indeed, substituting values obtained during anaesthesia paralysis for spontaneous breathing. Although, as discussed previously (Section 1.3), Crs and lung volume had been shown to be reduced in adults on induction of anaesthesia, knowledge of any such changes occurring in infants (and young children) was incomplete, there being no reported paired studies in spontaneously breathing infants.

Dobbinson (1973) had, however, reported a reduction in FRC of 35% in children aged between 6 and 18 years following the induction of anaesthesia. Measurements during anaesthesia were undertaken once the child was paralysed and receiving controlled ventilation (tidal volume 10 ml.kg\(^{-1}\)). With no suitable technique available to measure compliance pre operatively, Dobbinson was able only to obtain such measurements after the induction of anaesthesia.

MOT had already been shown to be applicable to both the sleeping and anaesthetised infant, and therefore a suitable technique to use to investigate further the relationship between Crs and anaesthesia in infants.

Two aims were identified:

1. To establish whether halothane anaesthesia caused a reduction in Crs in spontaneously breathing infants and young children similar to that previously reported in adults. Using the MOT, paired measurements of Crs were to be obtained during spontaneous breathing both pre and post induction of halothane anaesthesia.

2. If such a change in Crs did occur, to assess the extent to which it could
be reversed by paralysing the infant and manually ventilating with tidal volumes greater than those observed while the infant was breathing spontaneously during anaesthesia.

**Subjects**
Acceptance criteria were as described for Section 3.2, above.

**Methods**
Following administration of triclofos sodium at least 2 hours pre operatively, measurement of Crs in the sleeping infant was made as detailed in Section 2 (CrsS). This was completed prior to intramuscular injection of atropine 30 minutes before the induction of anaesthesia. At least one parent was always present during these measurements on sedated infants.

Following induction of anaesthesia, and tracheal intubation, as detailed in Section 2, CrsA was measured once tidal breathing was re established with a regular, stable tidal volume and frequency.

In 7 infants who were to be paralysed for surgical procedures (infants 56, 57, 61, 62, 76, 78, and 79), two further measurements were made:
1. during paralysis when ventilated with a low tidal volume mimicking that observed during CrsA measurement, (CrsLV), and
2. during paralysis when tidal volume was increased to at least double that observed during CrsA measurement (CrsHV).

This is described in greater detail in Section 3.2.

**Results**
Of 36 parents approached, only 1 refused permission for her child to be included in the study.

Measurements of Crs during sedation were therefore attempted in 35 infants. Four of the infants failed to sleep following sedation (one slept very briefly but then failed to relax during airway occlusion), and 8 failed to relax during airway occlusion.

Details of all the infants in whom measurements were unsuccessful are given in table 3.5. The extremely unstable EEL seen in 3 sedated infants (infants 34, 35, and 75) resulted in unreliable V - P data, such that these measurements had to be considered a failure.

The details of the individual results of the 17 infants successfully measured during both sleep and anaesthesia are given in table 3.6.

The V - P data for infant 73 is shown in Fig 3.9. This pattern of a reduction in Crs following induction of anaesthesia was seen in all but 1
Figure 3.9  V - P data for infant number 73, CrsA significantly less than CrsS.

Figure 3.10  V - P data for infant number 82, CrsA unchanged from CrsS.
Figure 3.11  Relationship between changes in Crs (expressed as percent of CrsS) and: a. body length,  b. age.
Figure 3.12  Tidal volume (a) and respiratory frequency (b) during both sedation and anaesthesia

Figure 3.13  Relationship between Crs and body length when spontaneously breathing during both sedation and anaesthesia
Figure 3.14  V - P data for infant number 62: CrsS, CrsA, CrsLV and CrsHV.
Figure 3.15  Crs (a) and tidal volume (b) for 7 infants in all 4 states, i.e. during measurement of CrsS, CrsA, CrsLV and CrsHV.
infant (infant 82), in whom Crs was unchanged (Fig 3.10).
The overall reduction in Crs was significant at p < 0.0001 (students paired t - test) whether based on % decrease (mean 34.7%), or absolute values (mean decrease 35.7 ml.kPa^-1). Furthermore in all but 3 of the infants the widely separated 95% CIs for Crs values in each state indicated highly significant changes in each individual (p < 0.05).
There was no relationship between the % reduction in Crs and the infant's age or body length (Fig 3.11).

**Tidal volume (Vt) and respiratory frequency (f).**
There was a significant fall in Vt (mean 42.5%) and increase in f (mean 61%) following induction of anaesthesia, p < 0.001 (students' paired t - test), see table 3.7, Fig 3.12.
However, there was no apparent relationship between either % fall in Vt, or % increase in f, and % fall in Crs. The change in minute ventilation varied from an increase of 22.3% to a fall of 45.8% (infants 78 and 56 respectively). Although there was an overall mean fall of 8.5% in minute ventilation (p = 0.04), there was no relationship between fall in Crs and change in minute ventilation.
Expressing minute ventilation per kg body weight, however, there was an overall decrease of 38 ± 69 (SD) ml.kg^-1.min after induction of anaesthesia. This was significant at the 5% level, although there was considerable inter subject variability (range +55 to -184 ml.kg^-1.min change).

**Changes in volume intercept.**
In 9 infants the volume intercept of the extrapolated V - P regression line changed by less than 1 ml.kg^-1 (see Sections 2.4 and 4.1). Thus in these 9 infants, anaesthesia appeared not to have resulted in any significant change in the extent to which FRC was dynamically elevated. In 4 of the remaining 8 infants the intercept changed by more than 2 ml.kg^-1 body weight following induction of anaesthesia, becoming significantly more negative in 3 (infants 37, 76, and 82) and less negative in 1 (infant 71). For all four infants, these changes were significant at the < 5% level, there being clearly seperated 95% CI for the intercepts in each case. The infant showing the greatest reduction in negative intercept, following induction of anaesthesia, from -5.15 ml.kg^-1 to -2.39 ml.kg^-1, also had one of the smallest increases in respiratory frequency (increasing from 48 to 50 breaths per minute).

**Growth and Crs**
The effect of growth on Crs was consistent in the sedated and anaesthetised states. Fig 3.13 displays Crs plotted against body length for the two states,
sedated and anaesthetised. Simple least squares linear regression analysis gave the following:

<table>
<thead>
<tr>
<th>Variance accounted for</th>
<th>Age</th>
<th>Weight</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrsS regressed against</td>
<td>76.5%</td>
<td>72.0%</td>
<td>84.7%</td>
</tr>
<tr>
<td>CrsA regressed against</td>
<td>67.5%</td>
<td>76.1%</td>
<td>76.3%</td>
</tr>
</tbody>
</table>

These values were not increased by regression following log. transformation of the data.

**Spontaneous breathing and paralysis.**

The V - P data from infant 62 for all 4 measurements of Crs are shown in Fig 3.14. The pattern of changes in Crs was similar in all 7 infants measured during sedation (CrsS), anaesthesia (CrsA), and anaesthesia paralysis with low and high tidal volume ventilation (CrsLV and CrsHV). CrsLV was similar to CrsA and increased to approximate values obtained during sedated sleep (CrsS) when tidal volume was increased (Fig 3.15).

Mean changes in Crs, tidal volume (Vt) and respiratory frequency (f) are shown in table 3.8A, expressed as a percentage of the values obtained during sedated sleep. Absolute values for Crs are collated in table 3.8B.

As found in the previous study, there was no significant relationship between respiratory frequency and Crs. The reduction in Crs which followed induction of halothane anaesthesia was reversed in all 7 infants, with high volume ventilation causing Crs to be as great, or greater than, Crs measured in the sedated, non intubated state.
Table 3.5 Infants in whom paired measurements of 
CrsS and CrsA were unsuccessful

<table>
<thead>
<tr>
<th>Infant number</th>
<th>Sedated (CrsS ml.kPa⁻¹)</th>
<th>Anaesthetised (CrsA, ml.kPa⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ML</td>
<td>TL</td>
</tr>
<tr>
<td>12</td>
<td>ML</td>
<td>FTR</td>
</tr>
<tr>
<td>22</td>
<td>FTR, ML</td>
<td>30.5</td>
</tr>
<tr>
<td>34</td>
<td>UEEL</td>
<td>47.9</td>
</tr>
<tr>
<td>35</td>
<td>Scatter (UEEL)</td>
<td>129.3</td>
</tr>
<tr>
<td>38</td>
<td>FTR, Woke</td>
<td>FTR</td>
</tr>
<tr>
<td>39</td>
<td>135.4</td>
<td>FTR</td>
</tr>
<tr>
<td>41</td>
<td>97.8</td>
<td>No time</td>
</tr>
<tr>
<td>42</td>
<td>FTR</td>
<td>FTR</td>
</tr>
<tr>
<td>43</td>
<td>75.3</td>
<td>FTR, SL</td>
</tr>
<tr>
<td>48</td>
<td>29.5</td>
<td>Cancelled</td>
</tr>
<tr>
<td>55</td>
<td>FTS</td>
<td>TL</td>
</tr>
<tr>
<td>58</td>
<td>54.0</td>
<td>Technical error</td>
</tr>
<tr>
<td>70</td>
<td>103.2</td>
<td>FTR, TL</td>
</tr>
<tr>
<td>75</td>
<td>UEEL</td>
<td>70.3</td>
</tr>
<tr>
<td>83</td>
<td>ML</td>
<td>FTR</td>
</tr>
</tbody>
</table>

**FTS** - failed to sleep  
**FTR** - failed to relax during airway occlusion  
**ML** - leak around the facemask during occlusion  
**TL** - leak around the tracheal tube  
**UEEL** - unstable end expiratory level

In addition 2 infants failed to sleep and were not followed through to the anaesthetic room, and 1 parent refused consent.
Table 3.6  Crs during sedated sleep and anaesthesia, breathing spontaneously

<table>
<thead>
<tr>
<th>Infant number</th>
<th>CrsS (ml.kPa⁻¹)</th>
<th>95% CI CrsS (ml.kPa⁻¹)</th>
<th>CrsA (ml.kPa⁻¹)</th>
<th>95% CI CrsA (ml.kPa⁻¹)</th>
<th>% fall in Crs</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>130.0</td>
<td>(112.5 - 147.6)</td>
<td>78.7 (51.5 - 88.9)</td>
<td>39.5</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>113.3</td>
<td>(85.7 - 140.9)</td>
<td>74.8 (62.7 - 86.9)</td>
<td>34.0</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>35.7</td>
<td>(30.1 - 41.4)</td>
<td>21.8 (20.2 - 23.4)</td>
<td>39.0</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>125.6</td>
<td>(120.1 - 131.1)</td>
<td>104.9 (98.0 - 112.5)</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>98.5</td>
<td>(93.0 - 103.9)</td>
<td>72.0 (62.5 - 81.6)</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>101.6</td>
<td>(87.8 - 115.5)</td>
<td>54.3 (51.5 - 57.0)</td>
<td>46.6</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>111.4</td>
<td>(103.2 - 119.8)</td>
<td>54.8 (50.0 - 59.7)</td>
<td>50.8</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>102.3</td>
<td>(96.1 - 108.6)</td>
<td>54.9 (48.4 - 61.3)</td>
<td>46.4</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>148.9</td>
<td>(142.9 - 155.0)</td>
<td>115.3 (108.8 - 121.9)</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>69.1</td>
<td>(60.0 - 78.2)</td>
<td>32.9 (29.6 - 36.0)</td>
<td>52.4</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>107.1</td>
<td>(88.6 - 125.7)</td>
<td>91.3 (79.6 - 103.1)</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>194.7</td>
<td>(180.5 - 208.9)</td>
<td>113.1 (89.2 - 137.1)</td>
<td>41.9</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>38.8</td>
<td>(33.7 - 44.0)</td>
<td>16.3 (13.3 - 19.2)</td>
<td>58.0</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>113.5</td>
<td>(90.1 - 137.0)</td>
<td>55.3 (49.3 - 61.3)</td>
<td>51.3</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>92.7</td>
<td>(80.7 - 104.7)</td>
<td>59.2 (51.1 - 67.1)</td>
<td>36.2</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>56.6</td>
<td>(49.1 - 64.0)</td>
<td>56.6 (48.9 - 64.4)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>164.8</td>
<td>(150.9 - 178.6)</td>
<td>142.4 (114.3 - 170.3)</td>
<td>13.6</td>
<td></td>
</tr>
</tbody>
</table>

CrsS Crs during sedated sleep
CrsA Crs during anaesthesia, breathing spontaneously
CI confidence interval
Table 3.7  Tidal volume, respiratory frequency, and volume intercepts of V - P data when sedated, and when anaesthetised.

<table>
<thead>
<tr>
<th>Infant number</th>
<th>CrsS Vt (ml)</th>
<th>CrsS f (bpm)</th>
<th>CrsS Int (ml.kg⁻¹)</th>
<th>% difference</th>
<th>Change in intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>108</td>
<td>25</td>
<td>-1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>98</td>
<td>30</td>
<td>-1.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>48</td>
<td>50</td>
<td>-2.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>102</td>
<td>30</td>
<td>-0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>100</td>
<td>28</td>
<td>-0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>78</td>
<td>36</td>
<td>-1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>81</td>
<td>48</td>
<td>-5.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>60</td>
<td>44</td>
<td>-3.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>125</td>
<td>23</td>
<td>-1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>70</td>
<td>40</td>
<td>+0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>85</td>
<td>30</td>
<td>-1.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>128</td>
<td>22</td>
<td>+0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>37</td>
<td>50</td>
<td>-1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>75</td>
<td>29</td>
<td>-2.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>80</td>
<td>29</td>
<td>-1.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>46</td>
<td>36</td>
<td>-0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>108</td>
<td>24</td>
<td>-0.96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CrsS - Crs during sedated sleep

CrsA - Crs during anaesthesia (breathing spontaneously)

Vt - tidal volume, f - respiratory frequency (bpm = breaths per minute),

Int - volume intercept on extrapolation of V - P data regression, ml.kg⁻¹ body weight

↓ - increase in negative intercept

↑ - decrease in negative intercept
Table 3.8 Respiratory compliance, tidal volume and respiratory frequency during sedation, anaesthesia, and anaesthesia paralysis in 7 infants. Results expressed as % sedated value.

A

<table>
<thead>
<tr>
<th></th>
<th>Crs (SD)</th>
<th>Vt (SD)</th>
<th>f (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>--------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>CrsA</td>
<td>59.8 (14.4)</td>
<td>54.9 (11.9)</td>
<td>169.5 (47.0)</td>
</tr>
<tr>
<td>CrsLV</td>
<td>63.4 (17.4)</td>
<td>52.2 (16.0)</td>
<td>166.5 (64.1)</td>
</tr>
<tr>
<td>CrsHV</td>
<td>102.6 (14.4)</td>
<td>121.7 (17.7)</td>
<td>129.4 (62.0)</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Infant number</th>
<th>CrsS (95% CI) m1.kPa⁻¹</th>
<th>CrsA (95% CI) m1.kPa⁻¹</th>
<th>CrsLV (95% CI) m1.kPa⁻¹</th>
<th>CrsHV (95% CI) m1.kPa⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>35.7 (30.1 - 41.4)</td>
<td>21.8 (20.2 - 23.4)</td>
<td>16.1 (15.1 - 17.1)</td>
<td>32.4 (28.1 - 36.7)</td>
</tr>
<tr>
<td>57</td>
<td>125.6 (120.1 - 131.1)</td>
<td>104.9 (98.0 - 112.5)</td>
<td>123.2 (109.1 - 137.5)</td>
<td>166.1 (154.6 - 177.5)</td>
</tr>
<tr>
<td>61</td>
<td>98.5 (93.0 - 103.9)</td>
<td>72.0 (62.5 - 81.6)</td>
<td>60.2 (56.3 - 64.2)</td>
<td>95.4 (87.8 - 103.0)</td>
</tr>
<tr>
<td>62</td>
<td>101.6 (87.8 - 115.5)</td>
<td>54.3 (51.5 - 57.0)</td>
<td>56.4 (51.2 - 61.6)</td>
<td>94.6 (90.5 - 98.6)</td>
</tr>
<tr>
<td>76</td>
<td>69.1 (60.0 - 78.2)</td>
<td>32.9 (29.6 - 36.0)</td>
<td>37.6 (30.5 - 44.7)</td>
<td>65.3 (46.0 - 84.6)</td>
</tr>
<tr>
<td>78</td>
<td>194.7 (180.5 - 208.9)</td>
<td>113.1 (89.2 - 137.1)</td>
<td>141.8 (136.6 - 146.9)</td>
<td>199.5 (178.2 - 220.8)</td>
</tr>
<tr>
<td>79</td>
<td>38.8 (33.7 - 44.0)</td>
<td>16.3 (13.3 - 19.2)</td>
<td>22.0 (21.1 - 22.9)</td>
<td>42.1 (39.3 - 44.8)</td>
</tr>
</tbody>
</table>

CrsS  Crs during sedated sleep  
CrsA  Crs when anaesthetised, breathing spontaneously  
CrsLV  Crs when anaesthetised and paralysed, tidal volume = that during CrsA measurement  
CrsHV  Crs when anaesthetised and paralysed, tidal volume = 2x that during CrsA measurement  
CI  confidence interval  
SD  standard deviation  
Vt  tidal volume  
f  respiratory frequency  

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Summary

Crs was measured both during sedated sleep (CrsS), and shortly after, following induction of anaesthesia (CrsA), in 17 spontaneously breathing infants.

In 7 of these infants, Crs was also measured during anaesthesia paralysis whilst being ventilated 1. with small tidal volumes (CrsLV) and 2. with tidal volume approximately doubled (CrsHV).

In all but 1 infant CrsA was less than CrsS, and in all 7 infants in whom measurements during paralysis were possible, Crs was returned to approximately pre-induction values during ventilation with high tidal volumes (CrsHV ≈ CrsS).

The results from this study indicate that a highly significant reduction in Crs occurs in spontaneously breathing infants and young children within 10 minutes of induction of halothane anaesthesia. The magnitude of the reduction in Crs (mean 34.7%) found in this study was similar to that reported previously in adults (Nims 37%, 1955, Gold 1965).

In the previous study (Section 3.2) it was shown that Crs during anaesthesia could be manipulated by altering the tidal volume administered to the paralysed infant. It appears that the reduction in Crs seen on induction of halothane anaesthesia could be reversed by paralysis and administering tidal volumes similar to those seen during sedated sleep.
Overall summary of Crs results

The cumulative results for all infants in whom at least 2 consecutive measurements of Crs were obtained (CrsS, CrsA, CrsLV, CrsHV) are summarised in Fig 3.16.

Pooling values for Crs obtained from all 56 infants in whom CrsA was measured successfully, the following regression equation was obtained:

\[ \log_e(CrsA) = 0.042L + 1.106 \quad (R^2 = 0.68) \] compared with

\[ \log_e(CrsS) = 0.043L + 1.475 \quad (R^2 = 0.80) \] from 23 sedated measurements, and

\[ \log_e(CrsS) = 0.049L + 1.038 \quad (R^2 = 0.89) \] from combined data of 3 studies on normal infants, Thomson 1985a, Marchal 1987, and Migdal 1987 (Davies 1990).

Figure 3.16 Crs during sedation and anaesthesia for all infants in whom at least two consecutive measurements could be obtained.
Table 3.9 Personal details of all infants

<table>
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<tr>
<th>Infant number</th>
<th>Age (months)</th>
<th>Length (cm)</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>Race</th>
<th>Diagnosis/Surgery</th>
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<td>anoplasty</td>
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Race: C Caucasian; WI West Indian; A Asian; M Mixed.

Diagnoses: PDA patent ductus arteriosus; TGA transposition of the great arteries continued...
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Race: C Caucasian; WI West Indian; A Asian; M Mixed.

Diagnoses: PDA patent ductus arteriosus; TGA transposition of the great arteries

Infants 51 and 53 length not measured at time of operation due to pressure of time. Infant 55 no successful measurements obtained.

continued...
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Race: C Caucasian; WI West Indian; A Asian; M Mixed.

Diagnoses: PDA patent ductus arteriosus; TGA transposition of the great arteries
Section 4

The multiple interrupter technique

Introduction
Measurements of total respiratory compliance (Crs) using the multiple occlusion technique (MOT) in spontaneously breathing infants can be difficult to interpret in the presence of an unstable end expiratory level (Section 2). Similarly, as discussed below, measurements using the passive flow volume technique (PFVT) are invalidated if there is alinearity of the expiratory time constant (i.e. in the absence of a single expiratory time constant), irrespective of the presence or absence of respiratory effort. As a possible means of overcoming these problems, the feasibility of measuring Crs using the technique of multiple interruptions of a single expiration (MIT) was assessed. The MIT relates several pairs of V - P data from a single expiration to a common end expiratory level, and does not require a linear flow - volume relationship during passive expiration.

In 1976 Olinsky and co-workers first published detailed data on the non-invasive measurement of Crs in spontaneously breathing infants using the airway occlusion technique. Since then, numerous adaptions to their technique have been developed and applied (Mortola 1982, LeSouef 1984a, Grunstein 1987). The measurement of total respiratory mechanics has now become a practical consideration in patients ranging from intubated preterm neonates to sleeping young children (Marchal 1987). Indeed recent reports suggest that such measurements may also be possible in awake toddlers and young children (Tangsrud 1991).

Based on evoking respiratory muscle relaxation during a brief airway occlusion, there are two predominant techniques used to date, the MOT (Section 2), and the PFVT (LeSouef 1984a).

The PFVT relates the equilibrated airway elastic recoil pressure, measured at the airway opening (δP) during an end inspiratory occlusion to the passively expired volume, extrapolated to zero flow, following release of the occlusion (δV).

\[
\text{Crs} = \frac{\delta V}{\delta P} \text{ ml.kPa}^{-1} \quad \text{Fig 4.1}
\]

The expiratory time constant of the respiratory system, Trs, can be
calculated from the slope of expiratory flow against expired volume, i.e. \[ Trs = \frac{Volume}{seconds} \]

Flow

Since \( Trs = Crs \times Rrs \), where \( Rrs \) = total respiratory resistance (Fig 4.1), both \( Crs \) and \( Rrs \) can be computed from the single occluded breath and subsequent passive expiration.

The PFVT can therefore be applied using the same measurement and recording equipment as the MOT, providing flow-volume plots can be created. The introduction of computerised data collection and handling provided this facility, allowing instant recall and plotting of collected flow and volume signals (Appendix A1).

While simple to apply to a wide range of infants, experience with these two techniques (MOT and PFV) has shown that the success of measurements may be limited in some infants by specific recurring problems.

In the infant with an unstable end expiratory level (EEL), Fig 2.10a, V-P data collected for the MOT tends to exhibit considerable scatter when plotted, increasing the variance of the slope, and thus reducing the certainty of the final result (Fig 4.2b). Under these circumstances, the time required to allow stabilisation of EEL between occlusions increases the likelihood of other factors, such as changes in sleep state, or waking, affecting the results.

The PFVT depends not only on relaxation of respiratory muscles during the occlusion, but also during the subsequent "passive" expiration. In addition, a single expiratory time constant is essential both to extrapolate volume to zero flow (for \( Crs = \frac{V}{P} \)) and to calculate \( Trs \), and thus \( Rrs \).

In infants failing to relax following release of the occlusion, and in those with linearity of the expiratory flow volume curve due to respiratory disease, the PFVT cannot be applied. This is true even in the presence of an adequate equilibration and relaxation plateau of airway pressure during occlusion.

In an attempt to decrease the time required for data collection and analysis for MOT measurements of \( Crs \), without dependence on a passive expiration with a linear flow volume relationship, as required for the PFVT, the possibility of performing multiple interruptions during a single expiration was re-examined.
Figure 4.1a  Passive Flow Volume Technique time based signals of volume and airway pressure. Airway occluded at the start of expiration.

Figure 4.1b  PFVT flow-volume plot, linear portion extrapolated to zero flow to obtain $\delta V$.

Figure 4.2a  Infant S1, variable EEL. Time based signals of tidal volume and airway pressure (see text).
Figure 4.2b  V - P data from infant S1 MOT. Scatter probably due to unstable EEL. Result from RASP (see text). Note wide 95% CI for slope.

Figure 4.3a  Multiple Interruptions of expiration, MIT. Tidal volume and airway pressure.

Figure 4.3b  V - P plot for MIT from data in Figure 4.2a, regression line added.
Initially described by Gottfried (1984a, 1984b), and used by his group to measure Crs in spontaneously breathing anaesthetised cats, and mechanically ventilated adults, the multiple interruption technique (MIT) has been applied more recently to measure Crs in spontaneously breathing anaesthetised children (Shulman 1988), but not sedated infants or young children. Multiple interruptions (brief occlusions) of a single passive expiration result in several pairs of V - P data which have a common EEL (Figs 4.3a and 4.3b). In theory, collecting data in this manner should result in more V - P points acquired over a shorter time period than for the MOT, thus reducing the variability of the data.

The aims of this study were:

a) to extend the use of the MIT to the measurement of Crs in sedated infants, including those with lung disease.

b) to demonstrate that the MIT was a suitable alternative to the MOT and PFVT when measuring Crs in infants and young children.
Section 4.1

Subjects
Measurements of Crs by MOT, PFVT and MIT were attempted in 16 infants, aged 0.5 to 20 months. Nine of these were healthy infants recruited for an epidemiological study which required full lung function assessment; the remaining 7 infants had been referred for lung function measurements for clinical reasons (table 4.1).

Section 4.2

Methods
All data were collected using a manually activated and operated shutter between a Rendell-Baker face mask and Fleisch pneumotachograph as described previously (Section 2). The shutter (design 2), which was controlled using a standard photographic cable release, had an opening/closing time of < 0.03 s. With practice, 6 to 7 complete occlusions per second could be performed, although this was more rapid than required for the purposes of the current study. Data display, recording and analysis were performed using RASP® software (Respiratory Analysis Program, Physio Logic Ltd) on a Compaq 386e deskpro computer (PC). An Analogue Devices' A to D expansion board was used to sample and convert the analogue flow and airway pressure signals into digital form before displaying on screen and saving to disk. Volume was digitally integrated from flow.

For the MOT, Crs was measured as described earlier (Section 2) (Stocks 1987). Using the manually operated shutter, brief airway occlusions during expiration were timed by observing the time base display of tidal flow, volume and airway pressure on the PC screen. At least 15 such occlusions were made throughout the first two thirds of expiration with 6 or more undisturbed breaths between each occlusion.

During data collection for the MIT, attempts were made to perform at least 4 brief interruptions of airflow (airway occlusions) during a single expiration, the first interruption being at the end of inspiration/start of expiration. A minimum of 5 such manoeuvres was performed for each infant allowing several uninterrupted breaths between occluded expirations.

PFVT measurements were attempted in all infants. End inspiratory
occlusions were held until airway pressure was seen to plateau before releasing. Where there was evidence of early inspiration or a non-linear relationship between flow and volume following release of such occlusions, their duration was reduced until more prolonged and/or passive (i.e. linear) expirations were seen to occur. Attempts were made to obtain 5 successful PFVT measurements in every infant, allowing 5 to 10 undisturbed breaths between occlusions.

The detection of leaks around the face mask during data collection was facilitated by allowing the EEL after an occluded breath to return to the pre-occlusion level, if necessary extending the time between interrupted breaths to allow this to occur (Section 2).

During data collection, both analogue inputs, flow and airway opening pressure, were sampled at 50 or 100 Hz for the MOT depending on the infant's respiratory rate. For MIT measurements sampling was initially set at 100 Hz during pilot studies but was subsequently increased for all infants to 200 Hz or occasionally 400 Hz, and the screen display scaled up to show each tidal breath in greater detail. Two infants, whose respiratory rates were < 15 breaths per minute, were measured at 100 Hz, the remainder at 200 Hz. When sampling at 200 Hz, the definition of the displayed signals was similar to that seen on chart recorder paper scrolling at approximately 75 mm.s⁻¹. For PFVT measurements analogue input sampling was set at 100 Hz.

Analysis

MOT data were analysed as described in Section 2, Crs being taken as the slope of the least squares regression line through the V - P data from all occlusions where airway pressure plateaus were ≥ 0.15 s (with standard deviation < 0.01 kPa for all samples over that period). An R² (squared correlation coefficient) of at least 0.9 was required before inclusion in comparisons.

MIT data were analysed as individual V - P slopes for each breath, providing there were at least 3 data points and R² ≥ 0.99. V - P data from an interruption were considered acceptable if there was a pressure plateau of at least 0.05 s with a standard deviation of <0.01 kPa in the samples over that period (10 samples at 200 Hz). The reported value for the MIT in each infant is the mean value of the individual V - P slopes for all technically acceptable breaths (minimum number of slopes = 2). For both MOT and MIT, Crs was only calculated when V - P data encompassed a pressure range of at
least 0.3 kPa.

PFVT data were accepted if the following criteria were met: 1) the linear portion of the expiratory flow-volume plot encompassed at least 40% of the total expired volume, 2) $R^2 > 0.99$ for the slope obtained by least squares linear regression of the flow-volume data, and 3) the pressure plateau samples had a standard deviation of <0.01 kPa over at least 0.1 s.

Differences in Crs values between the techniques were assessed for significance using students' paired t-test. As a measure of agreement between the MIT and the MOT and PFVT, the mean differences, the limits of agreement of the means, and 95% CI for the limits, were calculated, as described by Bland and Altman (1986).
<table>
<thead>
<tr>
<th>Infant number</th>
<th>Diagnosis</th>
<th>Age (months)</th>
<th>Weight (kg)</th>
<th>Length (cm)</th>
<th>Crs (ml.kPa⁻¹)</th>
<th>V int (ml.kg⁻¹)</th>
<th>Crs (ml.kPa⁻¹)</th>
<th>V int (ml.kg⁻¹)</th>
<th>Crs (ml.kPa⁻¹)</th>
<th>V int (ml.kg⁻¹)</th>
<th>Crs (ml.kPa⁻¹)</th>
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<td>S1</td>
<td>CW deformity</td>
<td>0.5</td>
<td>3.7</td>
<td>52.1</td>
<td>33.3</td>
<td>1.6</td>
<td>34.1</td>
<td>3.1</td>
<td>34.0</td>
<td>3.7</td>
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<td>54.6</td>
<td>1.1</td>
<td>55.4</td>
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<td>1.2</td>
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<td>2.1</td>
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<td>CMV bronch</td>
<td>6.0</td>
<td>6.0</td>
<td>65.0</td>
<td>39.8</td>
<td>1.4</td>
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<td>S13</td>
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<td>82.5</td>
<td>146.4</td>
<td>2.7</td>
<td>159.3</td>
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<td>184.1</td>
<td>5.0</td>
<td>160.8</td>
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<td>S14</td>
<td>YS tumour</td>
<td>20.0</td>
<td>10.5</td>
<td>82.5</td>
<td>128.9</td>
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<td>S16</td>
<td>C.myopathy</td>
<td>9.0</td>
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<td>70.3</td>
<td>77.2</td>
<td>3.1</td>
<td>-</td>
<td>-</td>
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<td>88.5</td>
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** Key to table 4.1 **

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CMV bronch</td>
<td>cytomegalovirus bronchiolitis</td>
</tr>
<tr>
<td>C.myopathy</td>
<td>cardiomyopathy</td>
</tr>
<tr>
<td>CW</td>
<td>chest wall</td>
</tr>
<tr>
<td>LCH</td>
<td>Langerhan cell histiocytosis</td>
</tr>
<tr>
<td>MIT</td>
<td>multiple interrupter technique</td>
</tr>
<tr>
<td>MOT</td>
<td>multiple occlusion technique</td>
</tr>
<tr>
<td>PFVT</td>
<td>passive flow volume technique</td>
</tr>
<tr>
<td>V int</td>
<td>volume intercept, ml/kg body weight</td>
</tr>
<tr>
<td>YS</td>
<td>yolk sac</td>
</tr>
</tbody>
</table>

** Crs 35.4 ml.kPa^{-1} calculated from merged data points using MIT (see text) **

* Crs predicted on body length (L) in cm, own data: $\log_{10} \text{Crs} = (0.049L + 1.038)$

Infants S6 and S14 are infants 4 (RE) and 3 (CD), respectively, in table 3.10, Section 3
Section 4.3

Results

The individual infants' results from measurements of Crs using all three techniques are shown in Table 4.1. Crs was measured successfully using the MIT in 14 of the 16 infants. Both infant S6 and infant S16, in whom this technique failed, had lung disorders. When measuring infant S6, who had CMV bronchiolitis, each interrupted breath resulted in only 1 to 3 V - P points over <0.3 kPa. For this infant, Crs could be calculated from the combined V - P data from all breaths where interruption had resulted in a satisfactory pressure plateau. This result was not included in any comparisons between techniques.

Infant S16, with severe cardiomyopathy, required < 0.3s for airway pressure to plateau during occlusion. Her respiratory drive, however, was such that inspiratory effort then prohibited further interruptions of expiration.

Two distinct patterns could be discerned in data from the MIT: 1) where the EEL was stable, the V - P data from different breaths were superimposed upon each other (Fig 4.4); and 2) where the EEL varied between measurements, the V - P data from each breath resulted in a series of parallel slopes (Fig 4.5). Interpretation of the data and identification of problems during the MOT, such as failure of airway pressure equilibration during occlusion, were comparable with the MIT. Fig 4.6 illustrates an interrupted breath from infant S10. During the initial interruption there was insufficient occlusion time for pressure equilibration to occur but data from subsequent interruptions were acceptable for analysis. Active expiration was evident in some breaths in certain infants resulting in the exclusion of those data from analysis (Fig 4.7). This problem did not occur in most infants, and at worst resulted in the loss of approximately 4 to 5 breaths out of a total of up to 10 attempts.

Failure of passive conditions due to possible abdominal and laryngeal muscle activity was illustrated by infant S2 (Fig 4.8). The breath illustrated in Fig 4.8a appeared well equilibrated during at least 4 of the interruptions. By the time the breath in Fig 4.8b was recorded, 4 minutes later, the infant's respiratory pattern had changed radically. From the volume trace it was apparent that airflow had been modulated, during both inspiration and expiration. This continued during the interrupted breath. The inappropriately low initial occlusion pressure may have been due to laryngeal muscle activity.
Figure 4.4  V - P data from 3 interrupted expirations (MIT), infant S11. Data all lies close to the common regression line.

Figure 4.5  V - P data from 4 interrupted expirations (MIT), infant S12. Each expiration represented by a different symbol. V - P points from different expirations form similar slopes with different intercepts. The variable intercept suggests a variable EEL.
Figure 4.6 Failure to achieve equilibration of P during initial interruption (MIT), infant S10. V = volume, P = airway pressure. Despite occlusion > 0.7 s, rapid equilibration during subsequent 6 interruptions allowed Crs (MIT) to be calculated. V - P data from final interruption excluded as inspiratory effort commenced.

Figure 4.7 Evidence of possible expiratory effort, MIT. Excluded from analysis. V = volume, P = airway pressure.
Figure 4.8  2 interrupted expirations from infant S2. $\dot{V}$ = flow, $V$ = volume, $P$ = airway pressure. Time of recording displayed in top right corner. Breath (a) recorded 4 minutes before breath (b). $\dot{V}$, $V$ and $P$ axes scales' identical in (a) and (b). Evidence of considerable respiratory activity before and during interrupted breath (b), as revealed by shape of $\dot{V}$ and $V$ recordings. Compare with flow in earlier recording (a).
activity. Complete glottic closure would cause pressure measured at the airway opening to represent only supraglottic pressure. Laryngeal adduction, by increasing resistance to airflow, may increase the time required for equilibration of airway pressure, thus preventing an equilibrated pressure being achieved within the duration of the interruption or occlusion. Gradual reduction in such laryngeal activity combined with some active expiratory effort would explain the increasing pressures and flows towards end expiration (Fig 4.8b).

As with the MIT, only one measurement using the MOT failed to obtain a value for Crs, due to unacceptable scatter of the V - P data from 13 satisfactory occlusions ($R^2 <0.9$). In this normal infant (number S15) the MIT was successful, and in infant S16 where the MIT had failed, the MOT was successful.

Of the 3 techniques, the PFVT was the least successful. In 5 infants it proved impossible to achieve, from the same breath, both a satisfactory pressure plateau during airway occlusion and a linear flow volume slope ($T_{rs}$) following release of the occlusions from any one breath. Values for Crs were obtained, however, for all 5 of these infants using the MIT or the MOT.

Consistent alinearity of the expiratory $T_{rs}$ (flow - volume plot) caused failure of the PFVT in one normal infant and in one with lung disease (infants S4 and S16). In both these infants Crs could be measured using either the MOT or the MIT.

When comparing the values for Crs obtained using all 3 techniques, the greatest differences were found between the PFVT and the other 2 techniques. Values for MOT and MIT should be similar since one is an adaption of the other, the advantages of the MIT lying in the reduced time required for data collection, and a reduction in the scatter of data points due to changes in EEL or sleep state between occlusions.

Crs as measured using MIT differed from that using the MOT by less than 9% in all 13 successful paired measurements. With so few infants, no trend in differences could be identified, associated with age, weight, or magnitude of Crs.

From table 4.2 it can be seen that, whether expressed in absolute terms or as percentages, there were no overall statistically significant group differences between the values obtained using the different techniques. However, when the differences were examined in greater detail, there was
found to be relatively poor agreement between the MIT and the PFVT (table 4.3). Although the group mean difference was less than 3% in all comparisons, individual differences varied from +26% to -16%, the greatest differences between Crs values tending to coincide with the greatest differences between the volume intercepts of the extrapolated V - P data (MOT or MIT) and extrapolated flow-volume data (PFVT), as illustrated by infants S3, S12 and S13 (table 4.1).

Table 4.2 Group differences between values obtained for Crs using MOT, MIT and PFVT

<table>
<thead>
<tr>
<th></th>
<th>absolute difference</th>
<th>% difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (range) ml.kPa^-1</td>
<td>p value</td>
</tr>
<tr>
<td>MIT - MOT</td>
<td>n=13</td>
<td>0.10 (-11.1 to 12.9)</td>
</tr>
<tr>
<td>MIT - PVFT</td>
<td>n=10</td>
<td>-4.76 (-31.1 to 8.9)</td>
</tr>
<tr>
<td>PFVT - MOT</td>
<td>n=11</td>
<td>4.41 (-13.0 to 37.7)</td>
</tr>
</tbody>
</table>

where p is the probability of the mean differences being zero.

p ≫ 0.05 in all cases, indicating that mean differences are not significantly different from 0, i.e. there is no significant difference between techniques.

Table 4.3 Limits of agreement between MIT and MOT, and MIT and PFVT

<table>
<thead>
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<th>techniques</th>
<th>mean difference</th>
<th>limits of agreement</th>
<th>95% CI</th>
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<td>MIT to MOT</td>
<td>0.10</td>
<td>-14.6 to 14.4</td>
<td>-21.4 to -7.6</td>
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<tr>
<td>MIT to PFVT</td>
<td>-4.76</td>
<td>-31.4 to 21.9</td>
<td>-46.1 to -16.8</td>
</tr>
</tbody>
</table>

Examining the data as suggested by Bland and Altman (1986), Crs obtained using the MIT may be up to 14.6 ml.kPa^-1 less than, or 14.4 ml.kPa^-1 greater than that measured for the same infant using the MOT (table 4.3). The limits of agreement are less good between the MIT and the PFVT (from -31.4 ml.kPa^-1 to +21.9 ml.kPa^-1), and the 95% CI for these limits of agreement illustrate further the relatively poor agreement between the two. The wide 95% CIs for the limits of agreement reflect in part the small sample size of this comparison.
Section 4.4

Discussion

The MIT has been applied successfully to measure Crs in the tidal volume range in sedated infants aged from 0.5 to 20 months. By obtaining more than one occluded V - P data point per expiration (Fig 4.3), the time required for data collection and analysis was reduced to approximately 30% of that required for the MOT. Absolute times varied depending on the infant's respiratory rate.

Failure rate for the MIT was the same as for the MOT, in terms of obtaining a value for Crs, but was greater for the PFVT, as discussed below. The cessation of respiratory activity during brief airway occlusion is thought to be due to the Hering Breuer Inflation Reflex (Olinsky 1974, Cross 1960). By maintaining the lung in a partially inflated state, pulmonary stretch receptors are stimulated and a transient apnoea evoked. Both post-inspiratory diaphragmatic activity and laryngeal adductor activity during expiration may increase the time between onset of occlusion and equilibration of airway pressure, even in the absence of disease. However, once equilibration has occurred, providing relaxation has been evoked, re-equilibration should be rapid following the release of a small aliquot of inflation volume, as during the MIT.

As described by previous authors, evoking a relaxed response to airway occlusion is least successful at lower lung volumes (Stocks 1987, England 1988). This frequently leads to a paucity of data at lower occluded volumes during the MOT. During the MIT, the respiratory system, having already been occluded at high lung volume, is in a relaxed and equilibrated state prior to the lower volume interruptions. This tends to result in more readily obtained and reproducible data at the lower end of the V - P slope than is usually possible when using the MOT, thus increasing the accuracy of, and confidence in, the resulting value for Crs. In this study 8 infants were more successfully occluded at low volumes during the MIT than the MOT, but the reverse was not true of any infant.

As a result of pilot studies, the minimum time considered adequate for an acceptable pressure plateau during the MIT was set at 0.05 s for two reasons: Firstly, after the initial equilibration period, very rapid re-equilibration was the normal pattern of response to repeat interruptions (Fig 4.3a). This was illustrated by data from infants measured during introduction of the technique where the second or subsequent interruptions were of longer
duration. These extended interruptions had the same characteristics as the shorter ones, showing an almost instant re-equilibration of pressure which was maintained in this stable state until inspiratory activity commenced or the occlusion was released. Expiratory or inspiratory effort was as easily detected as during the MOT, with a continually increasing or decreasing pressure during occlusion (Figs 4.7 and 4.8). The second reason for accepting short occlusions (and pressure plateaus ≥ 0.05 s) was the intention of achieving >3 interruptions per expiration. 0.05 s appeared to balance the need for sufficient data per interruption to facilitate the identification of potential problems such as expiratory effort, whilst maximising the possible number of interruptions per expiration. This decision was dependent upon the rapid sampling of signals (200 Hz) and the ability to view the data on an expansive time scale. The brevity of the pressure plateaus during the MIT was only feasible due to the pre-existing equilibration of airway pressure, and was therefore inappropriate for the MOT or PFVT.

Since V - P data from the MIT and MOT were closely comparable, and pressure equilibration is assumed to have occurred during successful MOT occlusions, it is reasonable to assume that equilibration had similarly occurred during the shorter MIT interruptions. This would suggest that the assumptions described above were valid.

Failure to achieve an adequate pressure plateau during the initial interruption using the MIT did not necessarily result in the loss of the complete interrupted expiration (Fig 4.6), as would apply to the MOT or PFVT. In many infants, initial equilibration of airway pressure during occlusion could take longer than 0.5 s. For infants S4 and S5 repeated attempts failed to achieve a linear Trs after an acceptable pressure plateau (which took > 0.5 s to occur) had been reached. As the duration of occlusion was increased in an effort to achieve a pressure plateau, so the incidence of expiratory effort or early inspiration also increased, causing failure of the PFVT. The PFVT in such infants was therefore more dependent on a rapid initial equilibration of airway pressure during occlusion, than either the MIT or MOT, to ensure a full passive deflation following release of the occlusion.

Although passive expiration following release of the occlusion was not a prerequisite for the MOT, the MIT required relaxation throughout the expiratory interruptions, and the PFVT a totally passive expiration. However, while the PFVT failed in infants S4, S5, S11 and S15 due mainly to failure to achieve airway pressure plateaus during occlusion, in all 4 infants the MIT
was successful. In these infants it appeared that even when an equilibrated pressure plateau and linear Trs could not be achieved in the same breath, the MIT could still be applied successfully. From the $V - P$ data from the MOT and MIT in such infants, it appeared that the respiratory system was in an equally relaxed state during airway occlusion for both techniques.

In infants with diseased lungs, particularly where respiratory resistance varies according to lung volume changes during the tidal breath, linearity of Trs is likely to occur, invalidating the PFVT. Thus even in the presence of a fully relaxed expiration, it may not be possible to obtain a linear Trs and hence Crs cannot be measured accurately using the PFVT.

In some infants a linear Trs, apparently devoid of expiratory effort and not foreshortened by inspiratory effort, could only be obtained during the PFVT when the preceding occlusion was too brief for an equilibrated pressure plateau. For such infants, the Trs thus obtained may be combined with Crs measured by either the MOT or MIT to compute a value for Rrs, since $Rrs = \frac{Trs}{Crs}$, as described by Mortola et al (1982).

Data from infants S12 and S13 highlight one of the problems peculiar to the PFVT. Any respiratory activity causing Trs to be altered from its true passive value will invalidate the volume (extrapolated to zero flow) measurement and thus Crs, since $Crs = \frac{V}{P}$. In infants S12 and S13, despite meeting or exceeding the inclusion criteria for all 3 techniques, Crs was much greater when calculated from the PFVT than when the MOT or MIT were used. Since $P$ at end inspiratory occlusion was similar for all three techniques, over-estimation of $V$ appears to have been the major contributor to this difference. In these 2 infants, extrapolation of volume to zero flow resulted in volume intercepts almost twice those from the other 2 techniques, thereby possibly doubling the correction made for the dynamic elevation of end expiratory level (England 1988).

In theory, differences in intercept between the MIT or MOT and PFVT could have reflected spontaneous changes in EEL, but had this been the case, in normal infants, the value for Crs should be essentially unchanged, assuming ventilation is still occurring over the linear portion of the $V - P$ curve of the respiratory system. The PFVT intercepts were calculated with reference to the end expiratory level of the preceding tidal breath, not the occluded breath. They are therefore directly comparable with the intercepts calculated for the MOT and MIT, and are not influenced by any premature
inspiration following release of the airway occlusion.

The greatest disadvantage of the MIT was the need for repeated short occlusions during expiration. In infants with a rapid respiratory rate and thus short expiratory time, this technique may fail to achieve sufficient V - P data to construct a single V - P line for each breath. Providing any changes in EEL are minimal, or can be corrected for by inspection of the time based recordings, V - P data from a number of breaths could be merged and Crs calculated as for the MOT. Data from infant S6 was analysed in this way, but excluded from any comparisons between techniques. The relatively large difference between the MIT and the MOT values of Crs for this infant may be a reflection of the greater scatter of V - P data from the MOT compared with the MIT, the latter having been collected over a considerably shorter time period.

If data are to be collected as for the MIT but it is anticipated that they may require merging as for the MOT, the principles of data collection for the latter should apply with respect to number of breaths between interrupted breaths. This should help prevent small changes in EEL from going unnoticed and increasing the scatter of the plotted data. Data collection may still provide more low volume data points, and should be more rapid than the MOT as more than one V - P point is collected per breath. Thus, although requiring more time than the MIT alone, merging the two decreases the likelihood of changes in the infant's respiratory pattern over time influencing the quality and quantity of the data. This attempt to minimise artifacts due to alterations in EEL should not be confused with true variability of the infant's Crs, since the latter is extremely unlikely to occur over the period of these measurements.

During measurements of Crs using the MIT in anaesthetised or ventilated subjects, expiratory time has been commonly extended for the acquisition of V - P data (Gottfried 1984b, Gay 1987). In this study it has been shown that this technique may be applied successfully to sedated, sleeping infants with respiratory rates of up to 63 breaths per minute. The MIT is particularly successful in the infant with a longer expiratory time as a greater number of V - P data points can be obtained per expiration. Potential problems encountered during the MOT appear to be as readily detected using the MIT.

Although respiratory muscle activity cannot be excluded from influencing this data, the reproducibility of the results within each infant and the close agreement with results from the MOT, suggest this did not occur. The use
of muscle activity sensors such as EMG's would be required to clarify this. The MIT offers a potential increase in the success of passive respiratory mechanics measurements in the non-anaesthetised infant. Used in conjunction with a measurement of Trs it may provide a means of assessing Crs, Trs and Rrs in the infant in whom the PFVT is unsuccessful.
Section 5

Discussion

Introduction

The interpretation of the results from this study depends upon the measurements being both accurate and a true representation of the parameter under investigation, total respiratory compliance. The thorough assessment of the measurement apparatus, as described in Section 2.1, should have ensured that all recordings of gas flow (and its integral, volume) and airway pressure were faithful representations of the physiological flows and pressures occurring during measurement sessions.

Of particular importance in this respect was the fact that the equipment was assessed as used, for measurements in both sedated and anaesthetised infants. This effectively ruled out any possibility of the measurements being influenced by factors such as the presence or absence of the anaesthetic bag and fresh gas flow.

As a result of these preparations, and the use of appropriate gases for calibration, any changes reported between Crs measurements should be physiological in origin, and not due to changes in equipment characteristics or calibration errors.

The second assumption, that Crs, as opposed to any other parameter, was being measured, depends upon the multiple occlusion technique being applied successfully. This in turn revolves around the principle assumption that, during airway occlusion, a pressure was generated within the closed respiratory system which resulted solely from the passive recoil of the lung and chest wall.

Following the strict criteria for data acceptance, as detailed in Section 2, all possible steps were taken to ensure that no data were included in analysis which may have introduced errors. The results reported in Section 3 should not, therefore, have been influenced by inaccuracies due to respiratory effort during airway occlusion, or due to air (or appropriate respired gases) escaping from the occluded system, by way of leaks around a poorly sealed face mask or tracheal tube.
Section 5.1

Methodology
This thesis has demonstrated that the MOT may be applied to measure Crs successfully in sedated, anaesthetised, and anaesthetised paralysed infants. However, certain practical problems had to be overcome, particularly with respect to leaks and controlling manual ventilation.

Leaks
The measurement of compliance using the MOT depended upon an accurate measure of the recoil pressure of the respiratory system and its associated occluded volume (above end expiratory level). If it was possible for air to leak out of the closed system during an occlusion, by-passing the pneumotachograph, the resulting airway pressure, measured at the airway opening, would have related to a smaller volume in the lung than that recorded. In effect, pressure would have been underestimated. In terms of a simple volume to pressure ratio, $\delta V/\delta P$, Crs would be overestimated in this situation. As leaks are frequently pressure dependent, they may only occur at higher occluded volumes (and therefore pressures). This would result in relatively greater distortion at the upper extreme of the V - P data. Fig 5.1 illustrates how the inappropriately low pressures recorded in the presence of a high pressure leak have resulted in gross distortion of the slope obtained by regression of the V - P data (Section 2). Had these data been accepted, Crs would have been grossly overestimated.

The escape of air through the shutter, due to incomplete closure, would also have resulted in inaccurate data, since pressure would again have been underestimated.

These examples illustrate how important it was to exclude from analysis any data which may have been influenced by leaks. Because of this, great care was taken to prevent leaks or, if missed at the time of data collection, to detect them during analysis and exclude any data so affected.

Any leak of air around a face mask was readily detected, and in only one infant (infant 83) did a small leak escape notice until data analysis. This high degree of success in eliminating leaks was due to the use of therapeutic putty around the mask rim, and ensuring that the EEL was restored following a test occlusion before launching fully into data collection.

Shutter leaks
The shutter in use during the initial data collection was designed specifically to provide minimal dead space. Despite thorough testing prior to every measurement session, this design proved unreliable in its ability to effect an
Figure 5.1 The effect on V - P data of a leak around the facemask or tracheal tube. At high pressures $\delta P$ is underestimated for the corresponding $\delta V$, resulting in an over-estimation of Crs.

Figure 5.2 Leak through the shutter during airway 'occlusion'. Note flow not zero, volume seen to alter, and airway pressure rises then slowly falls.
airtight seal during every occlusion. Such a leak through the shutter was manifested as a non-zero flow recording during the period of occlusion (Fig 5.2). Small leaks were difficult to detect during data collection using the UV recorder unless the leak was great enough to cause a visible fluctuation in the flow or volume traces on the oscilloscope. Using the computer (Appendix A1), any deviation from zero flow was immediately apparent from the position of the zero flow grid on the screen.

Although the new shutter design had a greater dead space than its predecessor, it had a much more reliable occlusion mechanism, compared with the original (design 1), and also tolerated autoclaving. The introduction of the new shutter immediately eliminated ineffective shutter seal as a cause of measurement failure.

**Tracheal tube leaks**

The tracheal tubes used in all infants described in this study were uncuffed (Section 2). To minimise air leaks, tubes were selected which resulted in a snug fit in the anaesthetised infants, in whom intubation was to be of short duration. Most small leaks in anaesthetised infants could be eliminated by applying gentle cricoid pressure. Despite such care, leaks which could not be eliminated did occur around tracheal tubes during some measurements. The problem of leaks tended to be greater in the infants measured for clinical purposes (Section 3.4), who had intentionally larger leaks around their tracheal tubes to minimise the complications of long term use. Infants with persistent leaks, in whom no reliable measurements could be obtained, represent an unavoidable failure rate of the technique (MOT). Cuffed tracheal tubes would have prevented all such failures, but the known risks to this age group of using cuffed tubes made it ethically unjustified to introduce their use for research purposes when not required clinically. The detection of leaks is discussed fully in Section 2.4.

In spontaneously breathing anaesthetised infants, the increased respiratory rates and decreased tidal volumes were usually associated with much more stable EELs than observed in sedated infants (Fig 2.10). This should have facilitated detection of air leaks during an occlusion, with a clear step-up in the volume trace following release of an occlusion. In practice, small leaks around the tracheal tube could be missed until the data were examined more closely after collection. This was particularly true when CrsS measurements in an infant with an unstable EEL were followed almost immediately by measurement of CrsA. In this situation the EEL may appear deceptively stable despite a small leak with a small step up in the volume (Figs 2.10a and b).
Figure 5.3  Active expiration during airway occlusion. P rises throughout the occlusion.

Figure 5.4  Apparent pressure plateau in the presence of a leak. On release of the occlusion EEL steps up, indicating loss of volume from the system during occlusion.

Figure 5.5  Progressive inflation during manual ventilation. Unlike the step-up in volume seen following release of an occlusion in the presence of a leak, following release of this occlusion expiratory volume is greater than inspiratory.
To time occlusions throughout expiration, adequate detail of each breath had to be displayed on the oscilloscope. This, in effect, limited the number of breaths per screen, visible at any time, reducing the ease with which a step-up in the volume trace could be distinguished from volume signal drift. The limited time available to complete these pre-operative measurements increased the likelihood of missing small leaks, particularly during spontaneous breathing and low volume ventilation, when occlusion and ventilatory pressures were low and any leak minimal.

In several spontaneously breathing infants, in whom airway pressure failed to equilibrate during occlusion, it was possible (although unlikely) that this may have been due to a small high pressure leak rather than the ascribed failure to relax (see below). Conversely, it was difficult to exclude the presence of active expiration in the presence of a definite leak.

Although a potential source of error, the measures described in Section 2, and discussed above, should have removed any possibility of leaks influencing the Crs results reported in this thesis.

**Measuring Crs during spontaneous breathing**

**The upper airway and Crs measurements**

Since the contributions of the larynx and pharynx to total respiratory system compliance have been shown to be minimal (Shulman 1988), the measurements of Crs reported here may be taken to represent the combined compliance of the lung and chest wall.

However, when measuring Crs in the non-intubated infant, shunting of gas from the lungs to the cheeks during airway occlusion could have resulted in erroneously low occlusion pressures being recorded. During occlusion, as pressure within the lungs increases, gas may flow from the lungs into the more compliant cheeks, causing these to inflate and the resulting equilibration pressure in the airways to be reduced. In effect, the lung volume would have fallen since the onset of the occlusion, and the recoil (equilibration) pressure would reflect this. However, as the volume lost from the lungs into the cheeks would remain within the closed respiratory system, and not pass through the pneumotachograph, it would not be possible to correct for the change in volume when calculating Crs. This situation, which is most likely to occur in the presence of very stiff lungs, could potentially lead to an overestimation of Crs, with inappropriately low pressures being related to any given volume above end expiratory level.

In all measurements using a face mask reported in this thesis, active
measures were taken to prevent or minimise any such shunting. The face mask was held in such a manner as to allow gentle supportive pressure to be applied to the cheeks. This effectively decreased their compliance to such an extent that preferential inflation of the lungs, rather than the cheeks, resulted, and there was no reduction of lung volume due to shunting of gas to the cheeks.

When measuring Crs in the intubated infant, such shunting of volume from the lungs to the cheeks would have required a leak around the tracheal tube. As the infants were orally intubated, with no attempt to seal the airway at the level of the lips, such shunting would have resulted in the loss of any such volume from the measurement system. This would have been manifested as a step up in the volume EEL following release of the occlusion (Section 2).

No expansion of the cheeks was seen during any measurements of Crs in intubated infants, and during analysis the data were carefully assessed for, and excluded in the presence of, any indication of a leak to atmosphere (Section 2.4). It was therefore extremely unlikely that such a mechanism influenced any of the measurements of Crs reported in this thesis.

When measuring CrsA, the problems encountered were similar to those associated with studying sedated infants but compounded by the more rapid respiratory rate following induction of anaesthesia (Section 2.4). As mentioned above, the pattern of breathing during anaesthesia included a much more stable EEL than seen in many sedated infants (Fig 2.10). This stability was reflected by the fact that no CrsA measurements were lost due to scatter of the V-P data from occlusions. In contrast, 3 measurements in sedated infants (aged 17.5 to 20 months) were unacceptable due to scatter of their V-P data as a direct consequence of instability of the EEL.

The presence of the tracheal tube during CrsA measurements prohibited modulation of expiratory airflow by upper airway muscle activity (Section 5.2). Such activity could have resulted in both an unstable EEL and non-equilibration of pressure between alveoli and airway opening during airway occlusion (Figs 2.18, 4.8b). Where there was any evidence of airflow being modulated in this way during CrsS measurement, data were rejected unless there was clear evidence that the activity was transient in nature, and airway occlusions had been performed during unaffected periods of tidal breathing.

The pressure plateaus were only accepted if they were clearly defined, rapid in onset (had been achieved within 0.5s) and were maintained throughout the
occlusion (or for at least 0.1s) or until there was an inspiratory effort. Any evidence of expiratory effort or delay in equilibration during the occlusion, as indicated by an increase in airway pressure after initial equilibration, resulted in the exclusion of data.

**Active expiration during spontaneous breathing.**
The presence of active expiration during halothane anaesthesia was responsible for the greatest proportion of failed measurements in spontaneously breathing infants. Increasing concentrations of halothane have been shown to reduce expiratory muscle activity in adults (Kaul 1973). By increasing the inhaled concentration of halothane to a maximum of 1.5% in infants who failed to relax during airway occlusion, the failure of measurements due to active expiration should have been minimised.
The problem of excluding expiratory effort as an influence on V-P data was common in all situations where the MOT was utilised to measure Crs during spontaneous breathing. Without the use of abdominal and rib cage EMGs, the potential presence of such activity has to be considered. However, applying strict acceptance criteria to the V-P data (see below), and obtaining reproducible values for Crs, suggest that such an influence on the data has probably been excluded.
The following factors were considered suggestive of expiratory activity during airway occlusion:
1. continually increasing P, no plateau (Fig 5.3),
2. an apparently rapid rise to a P plateau with a step up in volume baseline following release of the occlusion (a leak combined with expiratory effort, Fig 5.4),
3. a continuously changing P, rising to a maximum then decreasing as inspiratory effort commences (Fig 2.16).

Shulman (1989) demonstrated the presence of abdominal muscle activity during halothane anaesthesia in 8 of 10 children, aged 1.5 - 10 years (few of whom were younger than 2.5 years). Increasing halothane concentration abolished such activity in all but 2 normal children and one asthmatic. In this paper, Shulman described the effect of such activity on the passive flow volume technique (PFVT) for measurement of respiratory mechanics. The PFVT was assumed to be valid during sedation since there was no evidence of abdominal EMG activity during expiration in this state in 3 of the children. Unfortunately no mention was made of the P signal waveform, and as P plateaus were accepted if of at least 0.05 seconds duration, they would
in any case have been too short to assess for evidence of expiratory activity. Although confirming the recognised existence of expiratory activity during halothane anaesthesia in some subjects, Shulman's study does not, unfortunately, corroborate or refute the inspection of both the P and volume traces obtained during data collection as a means of detecting such activity (once leaks have been excluded). The incidence of unremitting expiratory activity found by Shulman in his group of older children (43.4%), was slightly higher than the incidence of failure to relax reported in the present study (30.3%). Thus, given that many of the anaesthetised infants demonstrated undeniable P plateaus during airway occlusion, and considerable data were discarded in other individuals, the data presented are felt to reflect a quasi-static state.

Infants who failed to relax (n=18) when measurements were attempted during spontaneous breathing tended to be younger than those in whom successful measurements were made (n=59). 10 (37%) of the 27 infants under 6 months of age in whom CrsA measurement was attempted failed to relax during occlusions, compared with 8 (16%) of those aged at least 6 months. This may have been related to the more rapid respiratory rates seen in the younger infants.

Further support for the validity of the CrsA measurements was given by the values for compliance obtained in the paralysed infants during low volume ventilation (CrsLV). Had active expiration been influencing CrsA pressure measurements, any effort would have been abolished during paralysis. Thus CrsLV would have been consistently higher (with lower airway pressures measured for the same change in lung volume) than CrsA. In fact there was no such difference, there being a mean increase of 6.6% (range -26% to +45%) with CrsLV being similar to CrsA in most infants (Section 3.2). This strongly supports the view that airway pressure data for CrsA were collected during relaxation of the respiratory system during airway occlusion.

Atropine and the Hering Breuer inflation reflex.

The strength of the Hering Breuer response to expiratory airway occlusion could be expected to be reduced in infants who had received atropine as pre-operative medication, due to the muscarine blocking effect of this drug. However, at the doses used in pre-medication such an effect has not been demonstrated, indeed Pisarri (1990) has shown very high doses of atropine to have little influence on vagally mediated responses to lung volume changes in anaesthetised dogs. It is unlikely therefore that atropine contributed to any great extent to the failure of some anaesthetised infants to relax during
airway occlusion.

In conclusion, although data were lost due to the intermittent or persistent failure of some infants to relax during airway occlusion, the collection of large amounts of data, careful examination of the time based traces, and rejection of all suspect data, yielded accurate results for both CrsA and CrsS measurements. However, the high failure rate of measurements of Crs using the MOT in spontaneously breathing infants anaesthetised with halothane makes this method of assessing respiratory mechanics inappropriate for routine use in this setting.

Measuring Crs during controlled ventilation
Measuring Crs in infants when they are both anaesthetised and paralysed has long been favoured over the spontaneously breathing or sedated states. In the data reported here, the greater success of measurements compared with those of CrsA was a reflection of there being no possibility of active expiration during airway occlusion in the paralysed infant. There was, however, a greater incidence of leaks around the tracheal tubes, particularly during high volume ventilation. During manual ventilation, the pressures applied to inflate the lung were in the range of 1 to 3 kPa. Although not excessive, the higher inflation pressures were greater than the pressures occurring during airway occlusion. In several infants there was evidence of a leak during lung inflation which was minimal or absent during subsequent airway occlusion and passive deflation. To allow for this loss of inflation volume, as measured by the pneumotachograph, passively expired volume following release of an occlusion was taken as the occluded volume above EEL and plotted against the equilibration P for that occlusion (Figs 2.9a, 2.14) Section 2.3.

Some early measurements were unsuccessful due to anaesthetists failing to ventilate manually with zero end expiratory pressure (ZEEP). Despite attempts to ensure a full passive deflation on release of the occlusion, both the extension of expiratory time and the total release of pressure within the anaesthetic bag were deviations from the familiar pattern of manual ventilation. The latter was characterised by a small though persistent level of positive end expiratory pressure (PEEP), as a consequence of maintaining a partially inflated anaesthetic bag in preparation for the next inflation. In addition, expiratory time was usually between 1 and 2 times the inspiratory time, not 3 to 5 times, as was required following Crs occlusions (thus
allowing at least 3 times the expiratory time constant for complete deflation to passively determined resting lung volume).

Fortunately the presence of PEEP was clearly evident during analysis of the recordings (Section 2.4). The position of zero airway pressure was recorded on the paper trace at the beginning and end of every study. Non return to this position following inflations or release of an occlusion, signified the presence of a positive pressure within the infant breathing system. During data collection using the original in-house amplifier, progressive inflation of the lungs of the paralysed infant due to inadequate expiratory time (Fig 5.5) appeared indistinguishable from electronic volume drift, a leak during inflation, or a combination of both. However, during the extended expiratory time post occlusion, the expired volume gave an indication of the extent of any progressive inflation (Fig 5.5). Data where PEEP was evident during passive deflations were discarded from analysis. Where minimal PEEP (<0.05 kPa) was present between inflations, providing this was released on airway occlusion, the data were accepted.

As will be evident from the above discussion, and inspection of the infant data in tables 3.2 to 3.8, Section 3, the success rate of obtaining technically satisfactory data improved with increasing experience. Several anaesthetists assisted with data collection and the success of measurements in the anaesthetised infants varied with the anaesthetist's ability to adapt to the different style of ventilation, and to interpret and respond appropriately to the signals displayed on the oscilloscope.

**Manual versus Mechanical ventilation.**

Although the pattern of ventilation would have been easier to control using a mechanical ventilator, there were several reasons why this was not considered appropriate.

In the original study design, one of the principle aims had been to assess the MOT as a simple method for measuring Crs in anaesthetised infants. The apparatus was designed to be equally applicable to any infant, during spontaneous or artificial ventilation. Adding a ventilator into a breathing system would not only have provided a means of ventilating the patient, it would also have completely changed the measurement conditions. Due consideration of, and compensation for, the following would have been necessary: 1) The compliance of the ventilator and its tubing, 2) probable pressurisation of the pneumotachograph, and 3) pressure variations resulting from the valve systems within the ventilator (Thomson 1983, 1985b, Le Soeuf 1984).
The success of measurements depended on the ability to eliminate PEEP totally, achieved in this study by venting the pneumotachograph to atmosphere. At the time this study was undertaken, the standard practice was to ventilate manually any anaesthetised paralysed infant until transfer into the operating theatre. Both pattern of ventilation and PEEP could be controlled using manual ventilation. There was therefore no indication for departing from normal practice by introducing a mechanical ventilator into the breathing system. This was important in minimising any disruption to normal anaesthetic practice, and maximising acceptance of the measurement team in the anaesthetic room.

Choice of measurement technique.

At the initiation of this study, two techniques for measuring Crs in spontaneously breathing infants were being explored. The MOT had proved successful in both intubated and non-intubated infants, (Thomson 1983, Stocks 1987). The PFVT (passive flow volume technique) had been shown to be less successful in neonates, unless the infant’s upper airway had been bypassed by tracheal intubation (England 1988). In addition the MOT was more simple to apply for technical reasons. During pilot measurements, the feasibility of using the PFVT to measure Crs as an alternative to the MOT was assessed. Measurements for this study commenced before the introduction of the computer into the recording system. During data collection, it was possible to view flow - volume (x-y) plots of the signals on the storage oscilloscope in real time, i.e. as they occurred. However, the additional equipment and time required to obtain hard copies of the plots, necessary to calculate Trs (and thus Crs), meant deferring the plotting until after leaving the anaesthetic room. Volume, flow and airway pressure signals were recorded on electro - magnetic tape at the time of the measurements, and later played back through the oscilloscope. Once a flow - volume plot of an occluded breath had been constructed and stored to the oscilloscope’s memory, the screen image was sent to a Hewlett Packard x-y plotter. Besides the data handling being tedious and cumbersome, the quality of data was adversely affected by any electronic drift of the volume signal. Such drift invalidated the relationship between flow and volume and thus could result in failure of the technique. Correcting for such a drift would have depended upon it being constant both in direction and magnitude throughout data collection. Due to the relative instability of the original electronics used in this study, eliminating electronic drift proved impossible. The drift also varied with time, although not during a Crs measurement session. In the light of the problems encountered by ourselves and others, the PFVT was
considered impractical for this study.
The comparison between the PFVT and the MOT and MIT (multiple
interruption technique, Section 4) was undertaken once the computer had
been introduced for the collection, storage, and analysis of data (Appendix
A1). When applied to measure Crs in the group of 16 non-intubated infants,
the failure rate of the PFVT was greater than that for either the MIT or
MOT. The principle cause of failure was the inability to obtain both an
equilibrated airway pressure plateau prior to release of the occlusion, and a
linear expiratory Trs (flow - volume relationship). This preliminary
comparison suggests that the problems described by England (1988) and
Guslits (1987), in obtaining a linear Trs in the non-intubated neonate during
the PFVT, apply equally well to the older infant.
It is probable that more potential paired measurements would have failed
during measurements of CrsS prior to the induction of anaesthesia, (Section
3), had the PFVT been used rather than the MOT.

Despite the high failure rate of the PFVT, when technically satisfactory data
were obtained there was close agreement between the measured values of
Crs irrespective of the technique used (MOT and PFVT values being within
10% of each other in 9 of 11 successful comparisons).
The similarity between the values for Crs obtained using these different
techniques suggests that, in these infants at least, the same parameter, Crs
was being measured. The underlying assumptions are different for the two
techniques (Section 4) and the calculation of Crs is based on different
parameters (V - P relationship for MOT, and flow - volume and pressure for
PFVT). This would therefore support the belief that, by applying strict
acceptance criteria to the data, Crs has been successfully measured in the
infants reported in Sections 3, 4 and 6 of this study.

Statistical methods and handling of data

Analysis of individual V - P data

Dynamic elevation of FRC
To prevent the underestimation of Crs by failing to take into account any
dynamic elevation of EEL above true passive lung volume, least squares
regression analysis was used to obtain the slope of the V - P data from
occlusions, as described in Section 2.4.
Under certain circumstances the duration of expiration may have been less
than was necessary for the lungs to deflate to true resting end expiratory
level. This could have occurred either as a result of short expiratory time (rapid respiratory rate) or raised expiratory resistance (impeding airflow). In this situation, inspiration would have begun before expiration was complete, with subsequent dynamic elevation of lung volume. When occluding the airway at end expiration a positive pressure would have developed within the closed airway, even in the absence of any muscle activity. This would have reflected the recoil pressure appropriate for the volume above passive FRC that remained in the lungs. Under these circumstances the whole slope of V-P data would have been shifted to the right with a positive intercept on the pressure axis and, if extrapolated, a negative intercept on the volume axis. This negative intercept has been taken to represent the extent to which end expiratory level is dynamically elevated (Mortola 1982, Thomson 1985a). Under these circumstances, Crs would have been underestimated if calculated as the mean of individual occlusion values,

\[
\frac{\text{occluded volume above end expiratory level}}{\text{airway pressure plateau}}
\]

From the data presented in Fig 5.6, the value for Crs from \(\frac{\delta V}{\delta P}\) for point 'a' = 93 ml.kPa\(^{-1}\). This would have underestimated Crs by 19% by not accounting for the true volume occluded above resting lung volume, of 60 + 14 ml.

In anaesthetised paralysed infants, where no muscle activity was present, Crs calculated by linear regression of multiple V-P data (MOT), should have been identical to that obtained by the simple division of the occluded volume, \(\delta V\), by occluded airway pressure, \(\delta P\), for each occlusion (Section 2), providing expiratory time was adequate for lung emptying to passive FRC following each occlusion. In other words, under these circumstances the regression should be linear and pass through the origin.

The presence of a significant volume intercept on regression of such V-P data would either have indicated elevation of lung volume above true resting level, due to previously undetected PEEP, or potential alinearity of the V-P data.

**Alinearity of V-P data plots**

During normal tidal ventilation (as during measurements of CrsS), infants are believed to breathe at a lung volume closer to residual volume than adults (Helms 1981). During low volume ventilation of the anaesthetised paralysed
Figure 5.6  Influence of the volume intercept on Crs calculated from V - P data. For point a Crs calculated by \( \delta V / \delta P \) is 93 ml.kPa\(^{-1} \), 19% less than the 115 ml.kPa\(^{-1} \) obtained by linear regression.

Figure 5.7  One possible explanation for the differences between CrsLV and CrsHV. During HV ventilation, tidal volume may have occurred over the central linear portion of the V - P curve of the lung (a), LV ventilation on the lower stiffer portion (b). TLC = total lung capacity, RV = residual volume, FRC = functional residual capacity; Vt = tidal volume, the portion of the V - P curve over which ventilation is occurring.
infant, the intention was to maintain the lung at approximately the same volume as during CrsA measurement. Halothane anaesthesia is known to result in a reduction in FRC (Westbrook 1973, Dobbinson 1973), suggesting both CrsA and CrsLV were measured at smaller lung volumes than CrsS. Normally, tidal breathing is assumed to occur along the linear portion of the V - P curve of the respiratory system. In view of the potential changes occurring to the lung as a result of anaesthesia, low volume ventilation, and then high volume ventilation, it is possible that ventilation could have been shifted to a linear portion of the V - P curve (Fig 5.7). Under such circumstances, the use of linear regression to calculate Crs would have been invalid. To be certain that a linearity of data did not influence the results in this study, the V - P relationship throughout the volume range of ventilation was examined closely. Before linear regression was performed, the scatter plots of the V - P data were checked (by eye) for any indication of linearity. A significant intercept on the volume axis resulting from the regression of V - P data collected from a paralysed infant would have been supportive evidence for such linearity. In all the results reported in Section 3, there was no evidence of linearity in any data from the measurement of CrsLV. In some of the early measurements of Crs in anaesthetised paralysed infants, there was some evidence that the upper portion of the V - P data may have been approaching linearity. However, the spread of V - P points was such that this may have been simple scatter of the collected data. In no individual was there evidence of linearity such that the value for CrsHV obtained as the regression coefficient of V - P data was not representative of Crs during the high volume ventilation.

Comparison between states.
The calculation of 95% confidence intervals for each value of Crs in all the infants was discussed in Section 2. When comparing changes in Crs between different ventilatory states, where the 95% CI for two Crs values did not overlap, there was a less than 0.05 probability that the difference occurred by chance. This increased the confidence with which an overall group difference between two values could be said to have existed (Chinn 1991).
Confidence intervals calculated for the regression coefficient, Crs, reflect the scatter and range of the V - P data used in the regression. Where data include a wide range of values of V and P, and lie close to the regressed slope, the 95% CI for the slope are very narrow, and small differences
between 2 slopes, such as those obtained for CrsS and CrsA, can be detected with confidence. Conversely, if the V - P data covers a narrow range of V and P, and/or lies widely scattered around the regression line, the 95% CI are wide, and any difference between two sets of data must be much greater before being confident that it is not due to chance (i.e. before the 95% CI no longer overlap, Fig 3.2).

In this thesis, the differences that were found to exist between CrsLV and CrsHV, measured in the same infants, were highly unlikely to be due to chance. For 19 of the 20 infants compared, the 95% CI for the two slopes, CrsLV and CrsHV, were clearly separated. In only one individual, infant 53, was there a slight overlap of the 95% CI. Similarly, between CrsS and CrsA, in most infants there was complete separation of the 95% CI for the two slopes. In 2 infants (infants 77 and 84) in whom the difference between the slopes was < 15%, there was some overlap of 95% CI, and for infant 82, where Crs remained unchanged between sedation and anaesthesia, the 95% CI for the two Crs values were virtually identical. In only one infant, infant 44, was there any overlap of CIs occurring with a large change in Crs (34%), this overlap being extremely marginal.

Thus, the group differences found between Crs values obtained in different states were a reflection of the highly significant changes taking place at an individual level.

When examining the data from other studies, such as those by Dobbinsion (1973) and Shulman (1988, 1989), interpretation of the results is hampered by a lack of reported information on the certainty of results within individual subjects.
Summary
1 The study of changes in Crs between sedation, anaesthesia and anaesthesia paralysis depended upon the accuracy of the measurement technique, and the same parameter (Crs) being measured in all states.

2 Air leaks through or around the infant measurement apparatus of face mask or tracheal tube, shutter, and pneumotachograph, would have invalidated results. Such leaks were not believed to have influenced the results reported in Sections 3.1 - 3.3, Section 4 and Appendix A1.

3 The shunting of lung volume to the cheeks during airway occlusion was minimised by applying cheek support.

4 Data were excluded from analysis if there was any indication that laryngeal activity was influencing the equilibration of airway pressure during occlusion.

5 Active expiratory effort was a greater problem during measurements in the anaesthetised infant than in the sedated infant. Although the results reported in Section 3 are believed to be free from the influence of such activity, this problem does indicate that the MOT and PFVT are unsuitable for routine use in spontaneously breathing anaesthetised infants.

6 In the absence of a mechanical ventilator with which PEEP can be controlled or eliminated, manual ventilation of the paralysed infant can yield successful measurements of Crs, following a period of training in the application of such ventilation. The use of manual ventilation also eliminates the problems of compliance within the anaesthetic circuit and ventilator.

7 The MOT could be applied successfully in all the states measured. This technique compared favourably with the PFVT, which at the time of study, would have been much more complicated to analyse, and which was subsequently found to have a higher failure rate than the MOT.

8 The significant decrease in Crs between sedation and anaesthesia (CrsS and CrsA), and the increase between low and high volume ventilation (CrsLV, CrsHV), was not only a group response, but also reflected significant individual changes in Crs, as determined by the 95% CI for each regression coefficient (slope).
Section 5.2

Sedation, Anaesthesia and Crs

The measured values for Crs obtained from the sedated infants in this study were very similar to those obtained from normal healthy infants both within this laboratory and by others.

Table 5.1 compares the prediction equation for CrsS obtained from the infants in the present study with that obtained from combining the original data from three studies on normal infants, Thomson 1985a, Migdal 1987, and Marchal 1987 (normal infants only) (Davies 1990). These are compared with the original prediction equations for normal infants obtained by Thomson (1985a), Migdal (1987) and Masters (1987).

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of infants</th>
<th>Age range</th>
<th>Prediction equation</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies 1990</td>
<td>&gt;100</td>
<td>0 - 24</td>
<td>(\log_{e} \text{Crs} = 0.049L + 1.038)</td>
<td>0.89</td>
</tr>
<tr>
<td>Present study</td>
<td>23</td>
<td>1 - 26</td>
<td>(\log_{e} \text{Crs} = 0.043L + 1.475)</td>
<td>0.80</td>
</tr>
<tr>
<td>Thomson 1985a</td>
<td>20</td>
<td>0 - 12</td>
<td>\text{Crs} = 2.24 \text{L}^{3.05} x 10^{-4}</td>
<td>0.96</td>
</tr>
<tr>
<td>Migdal 1987</td>
<td>20</td>
<td>&lt; 1</td>
<td>\text{Crs} = 2.67 \text{L}^{3} x 10^{-4}</td>
<td>*</td>
</tr>
<tr>
<td>Masters 1987</td>
<td>7(25)</td>
<td>1 - 12</td>
<td>\text{Crs} = 2.63 \text{L}^{3} x 10^{-4} + 0.87</td>
<td>0.88</td>
</tr>
</tbody>
</table>

* - not given

The equation quoted for Thomson is based on 24 measurements in 20 normal term and preterm infants, that for Masters on 25 longitudinal measurements in 7 infants. This, and the ages of the infants measured, should be taken into consideration when making comparisons between studies. Extrapolating any data to predict values of Crs for infants who lie outwith the range of the original measurements is particularly inappropriate. However, with this in mind, when applying these equations to predict values of Crs for infants of increasing body lengths, the values shown in table 5.2 were obtained.

Although the infants included in this study had pathology of varying type and degree, none had overt respiratory disease except those infants considered separately in Section 3.4.

The close conformity of values for CrsS in the present study with those obtained from normal infants with no evidence of disease, especially those from within this laboratory, suggests that the changes reported in this thesis may represent the response to anaesthesia and paralysis which could be expected of healthy infants.
When measured in the same spontaneously breathing infants, Crs during halothane anaesthesia (CrsA) was significantly lower than during sedated sleep (CrsS). Following the induction of anaesthesia, there was a mean reduction in Crs of 34.7% in the spontaneously breathing infants reported in the present study.
This was remarkably consistent with that reported to occur in adults.

Table 5.3 summarises the findings of 3 of the early studies in which paired measurements, when awake and during anaesthesia, were obtained in adults. Potential causes for these changes in Crs, Ccw and Cl following the induction of anaesthesia are discussed in Section 5.3.

The measurements of Crs and Ccw reported in studies on awake adults, summarised above, required voluntary relaxation of all respiratory muscles during expiration. Any respiratory activity during the phase of respiration being examined (i.e. inspiration and/or expiration) invalidates the resulting V - P data so obtained. Such a technique could not possibly be applied to awake or sedated infants and young children, and indeed, has proved difficult to teach to some adults (Van Lith 1967). This problem of ensuring complete relaxation during measurements of total compliance explains the dearth of such measurements in non-anaesthetised infants, and the very few published
comparative studies of compliance pre and during anaesthesia in adults. When measuring lung compliance (Cl) an oesophageal balloon was used to reflect dynamic changes in pleural pressure. Thus Cl measurements were not subject to the same dependence on the patients' ability to cooperate and perform a difficult manoeuvre as was the measurement of Crs. There are detailed discussions of the techniques used, and the reliability of the reported results, in the original papers (Gold 1965, Nims 1955, Westbrook 1973). Despite the potential problems, the results summarised in table 5.2 probably do reflect accurately the changes in compliance resulting from the induction of anaesthesia.

Volume History.

In anaesthetised, paralysed dogs, following hyperinflation of the lung to a pressure of 3 kPa for 5 seconds, dynamic lung compliance has been demonstrated to fall with time in the absence of further hyperinflation (with tidal volume 300 ml). This has been attributed to both tissue and surface force changes (Huang 88). In the animal model, there appeared to be a two-phase pattern of decline in Crs, with a rapid initial decline over the first 10 minutes, and a slower decline over the following hour. Ventilation with high tidal volumes (750 ml) did not prevent the initial fall in Crs, suggesting a possible lung tissue stress response to the hyperinflation. However, it did inhibit the subsequent, less rapid, reduction in Crs (Huang 1988).

The volume history given to the infants in this study consisted of several large inflations to a pressure of 2.5 to 3.0 kPa, maintained for less than 0.2s. This was similar to the large inflations usually administered by the anaesthetist to the infant following tracheal intubation. Had these initial large inflations evoked a similar stress response in the lungs of the infants to that demonstrated in animals, a decreasing Crs over time would have been expected during subsequent measurements, in all but those infants receiving repeated hyperinflations.

Spontaneous ventilation in the anaesthetised infant was characterised by a smaller tidal volume and more rapid respiratory rate compared with pre-anaesthetic values. A gradual fall in Crs during the period of measurement would have resulted in marked scatter of the V - P data, such that linear regression of the resulting points would have been inappropriate. In fact this was not the case in any spontaneously breathing, anaesthetised infant. During the subsequent paralysis and manual ventilation, Crs would be
expected to continue to fall, over the time period of the measurements, unless hyperinflation were arresting the decline (Mead 1959, Douglas 1969). During ventilation with low tidal volumes, the V - P data was remarkable for its linearity and the goodness of fit of the regression (high $R^2$, narrow 95% CI's), rather than for any scatter of the data. During high volume ventilation, following a volume history to 2.5 to 3 kPa, again Crs would have fallen with time, manifested as scatter of the V - P data. In practice, with 2 exceptions (Section 3.1), Crs was remarkably stable with time. This suggests that although the volume history may have reinflated parts of the lung previously poorly ventilated, it did not serve to hyperinflate the lung tissue to the extent that a stress response was evoked.

The changes in Crs reported in this thesis may be considered to be related primarily to the mode of ventilation at the time of measurement rather than the volume history administered prior to data collection. Although the possibility of a stress response cannot be ruled out entirely, there was no evidence in the data to suggest that a systematic fall in Crs was occurring. During the analysis of data from ventilated paralysed measurements, V - P data was measured and recorded on results forms in sequential order. Besides plotting the data as described previously (Section 2), the absolute value of $\frac{\delta V}{\delta P}$, i.e. an individual estimate of Crs, was also calculated. Since no dynamic elevation of lung volume should be present in the paralysed infant to cause this relationship to vary with occluded volume, the relationship should be constant throughout the measurements, subject to measurement error which should be unbiased and insignificantly small in nature. This assumes there was no alinearity of the data, which would also have resulted in a noticeable trend in the $\frac{\delta V}{\delta P}$ values, but one that was related to occluded volume rather than time of occlusion. By recording and analysing each occlusion in this manner, a sequential decrease (or increase) in Crs would have been detected immediately. In no infant could this be said to have occurred, except in the two infants reported previously (Section 3) in whom Crs changed as pattern of ventilation changed, during measurement.

**Volume dependence of Crs**

By paralysing the anaesthetised infants described in the present thesis, and ventilating them with tidal volumes approximating those observed during sedated sleep (Sections 3.2, 3.3), Crs was increased from that measured during spontaneous breathing (CrsA) in every individual, with a mean increase
of 62%.
The significant volume dependence of the Crs measurements in the paralysed
infants may explain much of the disparity between the results of earlier
studies reporting compliance measurements in anaesthetised infants and
children.

Many authors were aware of the potential influence of previous 'sigh'
inflations on subsequent values obtained for Crs in apnoeic anaesthetised
infants. In spite of this, little attention was paid to the inflation volumes
used during measurements of Crs, although these were recorded in some form
at the time of measurement, and often reported.
Particularly noteworthy in this respect are the studies by Lunn (1968), and
Richards (1961), reporting Crs measurements in apnoeic anaesthetised infants.

Allowing for differences between the techniques used, the values for Crs
reported by Lunn are almost half those found by Richards in a similar group
of infants. At end inspiration of a measured breath, Lunn's infants received
a lung inflation volume of between 3.5 and 12 ml.kg$^{-1}$ body weight.
At the start of measurements during deflation, Richards' infants had received
a lung inflation of at least 25 ml.kg$^{-1}$.
Tidal volumes during the measurements of Crs described in Section 3, and
summarised in table 5.4, were closer to those used by Lunn than Richards.
The largest tidal volumes, administered during measurement of CrsHV, were
still less than those used by Richards.

<table>
<thead>
<tr>
<th>Table 5.4 Tidal volumes (Vt) during Crs measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrsS n=17 mean Vt 10.2 ml.kg$^{-1}$ (range 7.4 to 13.9 ml.kg$^{-1}$)</td>
</tr>
<tr>
<td>CrsA n=30 mean Vt 5.4 ml.kg$^{-1}$ (range 3.3 to 8.4 ml.kg$^{-1}$)</td>
</tr>
<tr>
<td>CrsLV n=20 mean Vt 5.5 ml.kg$^{-1}$ (range 3.5 to 10.7 ml.kg$^{-1}$)</td>
</tr>
<tr>
<td>CrsHV n=20 mean Vt 11.9 ml.kg$^{-1}$ (range 7.7 to 20.3 ml.kg$^{-1}$)</td>
</tr>
</tbody>
</table>

where CrsS = Crs during sedated sleep, CrsA = Crs during anaesthesia, breathing spontaneously.
CrsLV and CrsHV = Crs during anaesthesia paralysis, with low and high volume ventilation
respectively.

Fig 5.8 shows the data for the present study compared with values of Crs
from individual infants from four previous studies on apnoeic anaesthetised
and a more recent study by Larsson (1989) reporting Crs for apnoeic infants
and Cl for spontaneously breathing infants.
Figure 5.8  Crs during anaesthesia compared with values of Crs from individual infants from five previous studies on apnoeic anaesthetised infants (Larsson 1989, Lunn 1968, Nightingale 1965, Reynolds 1966, and Richards 1960), and Cl from infants breathing spontaneously (Larsson 1989).
Figure 5.9 CrsLV and CrsHV compared with previous data collected from high and low volume inflations respectively (Nightingale 1965, Reynolds 1966).
Inclusion in this comparison was restricted to those individuals who fell within or near to the body length range of the present study i.e. all infants who were between 45 cm and 94 cm long. The relationship between Crs and body length can be seen to be maintained in all these studies.

Crs during paralysis is plotted in Fig 5.9, illustrating how the CrsLV and CrsHV data from this study agree most closely with previous data collected from high (Nightingale 1965) and low (Reynolds 1966) volume inflations respectively.

The two infants in whom CrsLV was remeasured, following CrsHV measurements, illustrate how immediate an effect reducing inflation volume had on Crs.

In reports of past studies, the authors have described large inflations being administered as volume histories between the induction of anaesthesia and measurements of compliance. Given the immediacy of the response to changes in inflation volume found in the present study, it is possible that the results obtained in the past tended to reflect the mode of ventilation at the time of data collection rather than any effect of the volume histories. Thus, Nightingale (1965), inflating infants' lungs to preset airway pressures for 10 seconds, reported higher values for Crs than those found by Reynolds, who used slightly lower inflation volumes maintained for only 1.0 seconds.

To date, there are few data available with which to compare the CrsA values obtained in the present study. Shulman has reported measurements in slightly older toddlers and young children, his findings indirectly supporting those of the present study, that Crs is reduced during halothane anaesthesia. Katayama (1984), measuring Crs and FRC in anaesthetised paralysed infants and young children, demonstrated an increase in Crs when lung volume was increased back up to 50% TLC, as predicted for non-anaesthetised, normal children. With simultaneous measurements of absolute lung volume and total respiratory compliance, Motoyama (1977), in an earlier study of anaesthetised paralysed infants and children, suggested that Crs corrected for lung volume was in fact very high in infants and decreased with age.
Summary

1. The values for CrsS obtained for the infants in the present study compare well with those reported by others for normal infants measured under similar conditions.

2. The reduction in Crs which occurred following the induction of anaesthesia, was of a similar magnitude, approximately 35%, to that previously reported in adults.

3. Although a decrease in Crs over time following large inflations has been described in adults and animals, measurements of Crs reported in this thesis are unlikely to have been influenced in this manner.

4. During anaesthesia paralysis, Crs demonstrated a marked dependence on the tidal volume being administered during measurements. This may in part explain the discrepancies between earlier reports of compliance measurements in anaesthetised paralysed infants.
Section 5.3

Anaesthesia and dynamic variation of lung volume.
In healthy non-anaesthetised newborn infants, lung volume is frequently maintained at a level above true passive FRC (Sections 2.4, 4.1). More recently this has also been demonstrated to occur in older infants (Thomson 1985, Colin 1989). The mechanisms employed to this end may be inactivated by the processes of anaesthesia and tracheal intubation. This in turn could exacerbate the effect of any reduction in lung volume resulting from anaesthesia.

Emptying of the lung during expiration may be delayed, and FRC elevated, by the presence of inspiratory muscle activity during expiration (Lopes 1981), or by active narrowing of the upper airway (Bartlett 1973, Mortola 1987).

The role of laryngeal muscles in reducing expiratory airflow may be present in many infants up to one year of age, although this need not necessarily result in dynamic elevation of lung volume (Colin 1989).

When measuring Crs in the sedated infants, occlusions were only accepted if the airway pressure plateaued within 0.5s (see Section 5.1), and were stable, with no subsequent increase in pressure for at least 0.1s. Although modulation of airflow could not be excluded in these infants without the use of laryngeal EMGs, any data where this was the case was probably discarded following examination of the airway pressure and the volume traces during analysis (Sections 2.4, 5.1).

During anaesthesia, upper airway activity has been shown to be inhibited in cats (Hwang 1983, Ochiai 1989), but this would anyway have been completely concealed in the measurements in anaesthetised infants in the current study due to the presence of tracheal tubes. These would have totally prohibited any influence of dynamic changes in upper airway resistance (narrowing) on lung volume. Post inspiratory activity during expiration has not been described in the anaesthetised patient, indeed, there is a tendency for the very lightly anaesthetised adult to exhibit active expiratory effort (Kaul 1973).

As described earlier, dynamic elevation of lung volume was taken into account when measuring Crs (Section 2.4, 5.1) and was reflected in the magnitude of the extrapolated negative intercept of the volume axis at zero airway pressure. To be valid, all measurements of Crs depended upon there
being no respiratory activity during airway occlusion. Such was believed to be the case in all measurements reported in this thesis. It is unlikely, therefore, that dynamic elevation of lung volume resulted from respiratory muscle activity, including that from the laryngeal muscles, in any of these infants. However, both tracheal intubation and anaesthesia may, in themselves, have resulted in a degree of elevation of lung volume. Resistance to airflow is inversely proportional to the $4^{th}$ power of the radius of the tube (with laminar flow). Since the lumen of a tracheal tube is less than that of the intact upper airway, the resistance to airflow is likely to have increased in all the anaesthetised infants in this study, compared with their non-intubated, relaxed state, as none of them suffered from pathological airway obstruction. In addition the tracheal tube will result in turbulence at lower gas flows. As peripheral airways resistance accounts for a relatively small percentage of total airways resistance (Taussig 1982), reducing the lumen of the infant's (narrow) upper airway by even a small amount may have resulted in a significant increase in total resistance (Rrs) (LeSouef 1984b).

Such an increase in Rrs would have increased the time constant of the respiratory system, $T_{rs}$, according to the equation $T_{rs} = Crs \times Rrs$. Thus, all other things being equal, a longer expiratory time would have been required to allow complete emptying of the lungs to passive FRC (at least 3 x $T_{rs}$) following intubation, unless $Crs$ decreased exactly in proportion to the increase in Rrs. Providing respiratory rate was such that expiratory time remained greater than 3 x $T_{rs}$, lung volume would not necessarily be increased dynamically even in the presence of increased Rrs. However, an increase in respiratory frequency (mean increase 61%), with a consequent decrease in expiratory time, was recorded for all these infants during anaesthesia when spontaneously breathing. This combination of an increase in respiratory resistance and reduced expiratory time could potentially have resulted in considerable elevation of lung volume, had $Crs$ not been reduced during anaesthesia.

In fact only 3 infants, (infants 71 and 72 during sedation, and infant 37 during anaesthesia when spontaneously breathing), had volume intercepts greater than 3 ml per kg body weight when their V - P data were analysed. In 3 infants, (numbers 37, 76 and 82, the intercept increased by more than 2 ml per kg after induction of anaesthesia and tracheal intubation. In only 1
infant (number 71) did the intercept decrease by more than 2 ml per kg. The smaller than average increase in respiratory frequency shown by infant 71 when anaesthetised (4%), combined with a 50.8% decrease in Crs, may have resulted in a loss of dynamic elevation of lung volume, as reflected in the reduction of the volume intercept by 20 ml, compared with the sedated state.

These changes in intercept between CrsS and CrsA were not accompanied by any trend in the magnitude of the reduction in Crs following induction of anaesthesia. For infants 37, 76, and 82 (intercepts increased by > 2ml.kg⁻¹), and infant 71 (intercept decreased) respectively, Crs was reduced during anaesthesia by 39.5%, 52.4%, 0.0% and 50.8%. It is therefore unlikely that intubation per se was primarily responsible for the observed reduction in Crs following induction of anaesthesia.
Section 5.4

Anaesthesia and lung volume
Besides the reduction in Crs reported to occur as a consequence of the induction of halothane anaesthesia in adults, and demonstrated in the present study in infants and young children, FRC has also been shown to fall (Section 1).

The role of the chest wall in determining FRC and Crs has been discussed previously (Section 1), and would lead one to anticipate a reduction in Crs during halothane anaesthesia since the inward recoil of the lung would be working against a less effective outward recoil of the chest wall. The altered contribution and configuration of the rib cage and diaphragm may also influence the V - P relationship of the enclosed lungs within.

These changes in lung volume and compliance are inextricably related.

Although there remains considerable uncertainty and debate about the true cause and effect of changes in thoracic volume during anaesthesia, certain changes are known to occur.

Muscle tone, thoracic configuration and blood volume
The major influence is probably the loss of tonic muscle activity of the intercostal muscles and diaphragm during anaesthesia (Jones 1987). The increase in abdominal muscle tone, particularly of the abdominal oblique muscles, during expiration may further reduce FRC, until such activity is diminished or abolished by increasing depth of anaesthesia (Kaul 1973, Freund 1964).

Possibly as a result of these changes in muscle tone, rib cage impedance is greater during anaesthesia with spontaneous breathing than it is when either anaesthetised, paralysed and receiving artificial ventilation (IPPV, with tidal volumes approximating normal, non-anaesthetised values), or when not anaesthetised (lying supine) (Rehder 1990).

In adults, the increase in intrapleural pressure that occurs on paralysis and IPPV is more closely coupled to the rib cage than the abdomen, i.e. the rib cage contribution to chest wall movement is greater during IPPV than during spontaneous breathing (Grimby 1975, Rehder 1986).

In infants, the contribution of the rib cage to inspiratory effort increases gradually from birth up to the age of about 9 months, by which time the adult pattern has become established (Hershensen 1990).

Profound depression of rib cage activity during halothane anaesthesia has been demonstrated in children aged 6 years and above (Tusiewicz 1977),
although Brown (1992) failed to demonstrate such marked changes in non-intubated anaesthetised infants and young children. Benhameur (1992), studying a similar group of patients, found the younger infants to have more asynchrony between rib cage and abdominal movements, for the same concentration of inhaled halothane, than children over 12 months of age. During quiet sleep, the infant’s ventilatory response to CO₂ breathing appears to depend more on the rib cage than the diaphragm, and it has been postulated that this acts to preserve the diaphragm in its most efficient configuration (Hershenson 1989). This response may have been severely compromised during halothane anaesthesia with the reduction in rib cage tone.

Chest wall compliance is considerably greater in the infant than in the adult. Any further reduction in chest wall tone due to the effects of anaesthesia may therefore have been expected to result in a marked fall in FRC. The loss of outward recoil of the rib cage, and the consequent reduction in the stability of the chest wall, would have potentiated the inward recoil of the lung, predisposing to atelectasis and small airway closure or collapse.

Active expiratory effort resulted in the failure to measure CrsA in 18 infants, as discussed in detail earlier (Section 5.1). The presence of expiratory muscle activity in spontaneously breathing anaesthetised subjects has been documented in adults and children, using abdominal EMG recordings (Freund 1964, Kaul 1973, Hewlett 1974, Shulman 1989). Such activity would be expected to potentiate any reduction in FRC during anaesthesia. Hewlett found that the presence of phasic expiratory muscle activity bore no relationship to the decrease in FRC following the induction of anaesthesia. Since FRC is reduced during anaesthesia irrespective of the presence of expiratory muscle activity, this would suggest that the latter may potentiate, but is not the principle cause of, the reduction in FRC.

Besides the changes in muscle tone and activity, the causes of the reduced FRC in anaesthetised adult patients may include: - cephalad movement of the diaphragm, which has been shown to be greater in the prone than the supine position (during anaesthesia); decrease in cross-sectional area of the ribcage; and movement of blood volume into, or out of, the thorax (Froese 1974). The contribution made by each of these to the reduction in FRC in adult subjects remains subject to debate. Using state of the art technology, Hedenstierna and colleagues in Upsala, Sweden, and Krayer and colleagues at
the Mayo clinic in the USA have used different measurement techniques with conflicting results. Hedenstierna using Computed Tomographic (CT) scans found a cephalad displacement of the diaphragm which could account for an estimated reduction in FRC of 500ml. Using direct measurement of blood volume in adults, Hedenstierna’s group also suggested that anaesthesia with halothane resulted in a decrease in central blood volume of 300 ml (Hedenstierna 1985). Krayer (1987), using three dimensional spatial reconstruction (of multiple X-ray projection images), found that cephalad displacement of the diaphragm did not contribute significantly to the 500-600 ml reduction in FRC resulting from anaesthesia. From Krayer’s measurements, anaesthesia appeared to be accompanied by a net increase in thoracic blood volume.

The disparity between the findings of these two groups may be attributable to the different techniques used, and assumptions applied. In infants and young children, very little is known in this area. Measurements such as those performed on consenting adults by Hedenstierna and Krayer remain ethically unacceptable in this age subject. In view of the structural differences between an infant’s thorax and that of an adult (both in configuration and mechanics), any changes in diaphragm function and blood volume distribution due to anaesthesia may also differ. The measurements of respiratory movement such as those made by Tusiewicz (1977) and Brown (1992), and their conflicting results, make it difficult to predict the behaviour of the diaphragm in anaesthetised infants, although any cephalad movement may be limited by the more horizontal configuration of the thorax in infants.

Whatever changes do occur, the functional efficiency of the diaphragm would be influenced by any alteration in the configuration of the thorax, due to any cause. This would affect the cross sectional area of action and the relationship between rib cage, crural and abdominal diaphragm. In infants the thoracic cavity is less efficient than in adults in terms of ventilation (Openshaw 1984). Any further reduction in support to the thorax by the rib cage would serve to enhance any deleterious effects.

**Atelectasis during anaesthesia**

Atelectasis has been postulated as a possible cause of the reduction in lung volume, seen in anaesthetised man, since 1959 (Mead). However, it was not until the mid 1980's that the presence of atelectic areas in the lung were
demonstrated clearly by Hedenstierna and colleagues. Using CT scans, in human volunteers and patients, and post mortem examinations of animal models, Hedenstierna's group demonstrated the following:

1. atelectasis develops in dependent regions of the lung during anaesthesia.
2. atelectasis is only partially reversed by mechanical or manual lung inflation.
3. the abnormal gas exchange which occurs during anaesthesia is closely related to the extent of the atelectasis.
4. anaesthesia with ketamine, which preserves the tone of the respiratory muscles, does not appear to result in atelectasis.
5. atelectasis persists for longer than 12 hours into the postoperative period in some patients.


In addition, Heneghan (1985) demonstrated that PEEP or phrenic nerve stimulation both reduced atelectasis to a greater extent than did IPPV. Damgaard-Pedersen (1980) demonstrated densities in the dependent areas of the lung in anaesthetised, but not sedated, children. These densities were of the same location and form as those described in anaesthetised adults by Hedenstierna's group, which later ascribed them to atelectasis, as described above.

The formal study of such physiological changes in children is severely curtailed by ethical considerations. However, it would seem appropriate to extrapolate, with due caution, the findings in adults back to children. Damgaard-Pedersen's observations suggest that areas of atelectasis do form in the dependent regions of the lungs in anaesthetised children. However, the differences in contribution to ventilation made by the rib cage, diaphragm, and abdominal muscles between the small child and the adult may result in a different pattern of disturbance, both in magnitude and location (Openshaw 1984, Hershenson 1990).

**The role of surfactant**

The formation of atelectic areas in the lung during anaesthesia is probably due to a combination of the loss of outward recoil of the chest wall, and increased inward recoil of the lung, lung compliance having been shown to fall by up to 50 % in adults (Westbrook 1973).
The changes in lung volume due to halothane anaesthesia are accompanied by changes in lung tissue characteristics, particularly with respect to surfactant and surface tension. Despite this, the role of surfactant in determining lung volume and compliance during anaesthesia is unclear. It may, however, play a more important part than was previously thought.

Within the lung, the maintenance of a large surface area, and minimal tissue barrier for efficient gas exchange, depends crucially on the following:
1. the connective tissue scaffold on which capillaries and the alveolar surface are suspended.
2. the activity of the lining cells of epithelium and endothelium forming active barriers for fluid exchange.
3. the secretory function of type II cells producing adequate surfactant phospholipids to reduce surface tension to tolerable levels.
(Weibel 1986).

Under normal conditions, the surface tension of the alveolar lining liquid increases as alveoli enlarge, and surfactant molecules become further apart, and decreases as they shrink. Thus, all sizes of alveoli exert almost the same pressure, stabilising their inter-relationship (Widdicombe 1989).

The pressure volume curve for an air filled lung results from a combination of tissue and surface tension effects, and shows 4 phases:
1. high pressures are needed for the initial inflation of collapsed alveoli.
2. at the critical opening pressure, ≈1 kPa in adults, maintained inspiratory effort results in the inflation of a large part of the lungs.
3. as inspiratory capacity is approached, greater inflation pressures are required to increase lung volume further.
4. alveoli tend to remain open on deflation, emptying at lower pressures than were initially required for inflation.

Anaesthesia may disturb the fine balance between surface tension and lung inflation characteristics in several ways. Changes in thoracic muscle tone and blood volume are likely to alter the structural support of the alveoli. In addition, changes in smooth muscle tone in the conducting airways, which occur during anaesthesia, have been shown to alter lung compliance (Mitzner 1992). Cell secretory function has been shown to be adversely affected by the noxious gases of anaesthesia, by high pressures of mechanical ventilation,
and by ventilation with very large or small tidal volumes, particularly after lung injury (Woo 1970, Rehder 1986, Parker 1990, Carlton 1990). Although these effects have been demonstrated in animal, not human, subjects it is possible that similar mechanisms may have altered the characteristics of the surface fluid of the lung, and also surfactant production, in the anaesthetised infants described in Section 3.

In the presence of reduced structural support and/or reduced surfactant efficiency, greater pressures would have been required to inflate the lungs, irrespective of any changes in absolute lung volume. By their very nature, changes such as these would also tend to cause lung volume to fall.

Surfactant may also play a critical role in preventing small airway collapse. In a recent report, Liu (1991) has elegantly demonstrated how important surfactant may be in maintaining small airway patency. Using small tubes Liu assessed surface tension forces of different fluids, and their tendency to obstruct free airflow through very narrow tubes. These tubes were of the order of 0.4 mm internal diameter, slightly larger than an adult's terminal bronchiole, whereas a terminal bronchiole in a newborn infant may be as small as 0.1 mm in diameter (Hislop 1989).

The volatile anaesthetics have been shown to disturb surfactant secretion and distribution in adults, with rapid recovery on removal of the insult.

It follows from this that any disturbance of the surfactant film lining an infant's small airways may increase the tendency of such airways to collapse, particularly in the presence of atelectasis. In this situation, considerable force would be required to re-establish airway patency since there could be little contribution towards reinflation from the distal, collapsed, airway (Martinez 1991).

Peripheral airways depend principally upon the elastic recoil of the lungs to maintain their patency. In infants, their very compliant chest wall is associated with a lower FRC : TLC ratio, and thus a lower elastic pressure (Pel) at FRC (Helms 1981). Pel is less subatmospheric in infants than adults, decreasing the stability of peripheral airways (Martinez 1991). Liu's findings support the early reports from Macklem (1970), that the influence of surfactant extends from alveoli to peripheral airways, thus helping to prevent premature airway closure, and that the local inactivation of surfactant may predispose to airway closure.
**Surfactant and lung volume**

Ventilation at low lung volumes has been shown to deleteriously affect surfactant function in animals (Young 1970), and large inflation volumes to inhibit surfactant function (Bachofen 1968). Although this may also have been influencing the very low values for both CrsA and CrsLV, when inflation volumes were small, to be a major contributor to the changes observed on alteration of pattern of ventilation during IPPV, surfactant function would need to have responded as rapidly as Crs to the changes in tidal volume. Since CrsHV was measured during ventilation with tidal volumes similar to those seen during sedated sleep, it is unlikely that inflation volumes were of the order required to inhibit surfactant function.

**Anaesthesia, atelectasis, lung volume, and Crs.**

Atelectasis of dependent regions of the lung may reduce compliance by two mechanisms. Firstly the reduction in total lung volume due to anaesthesia will result in a reduced gradient of the V - P curve of the respiratory system, as discussed below. Secondly, with a reduced absolute lung volume and totally collapsed areas in dependent regions of the lung, ventilation will occur at, or very near to, closing volume. During anaesthesia, the reduction in absolute lung volume, accompanied by atelectasis, will result in a smaller inflatable total lung capacity composed of fewer distensible units than in the pre - anaesthetised state. Thus the characteristics of the whole V - P curve will alter, since greater initial distending pressures will be required. Unless more alveoli are recruited, to increase potential lung volume, higher pressures will also still be required for subsequent inflations.

Besides allowing for the concomitant changes in chest wall tone, this pattern is consistent with that already demonstrated in adults, in whom paralysis caused no further reduction in lung compliance (Fig 5.10). Such a scenario would explain the differences found between measurements of CrsS and CrsA in the present study.

When the infants were paralysed, and in the absence of large inflations, Crs remained low with respect to CrsS values. This may have been a reflection of the fact that absolute lung volumes remained essentially unchanged from those during CrsA measurement. During manual ventilation when paralysed,
Figure 5.10 V - P curve of the lung and chest wall during anaesthesia and anaesthesia paralysis. (From Westbrook 1973). During anaesthesia the V - P curve of the respiratory system is both shifted to the right and less steep (less compliant). Paralysis results in little further change.

Pao = pressure measured at the airway opening (alveolar pressure in the absence of flow), Ptp = trans - pleural pressure, Poes = oesophageal pressure, TLC = total lung capacity.
although the diaphragm - ribcage relationship may have changed, there was no measured net effect of paralysis on Crs.

Large inflations, shown to improve Crs in adults (Section 1, also Grimby 1975), had a similar effect on Crs in the infants in the present study. Several mechanisms may have been involved in this improvement. The application of PEEP has been demonstrated to open collapsed alveoli (Tokics 1987b). Large inflations may have a similar effect. In the preliminary study discussed in this thesis (Section 3.1), Crs increased progressively with time when infant 34 was ventilated manually with vigorous inflations. This may have been due to progressive lung expansion with increasing recruitment of previously collapsed alveoli.

In addition, the significant increases in tidal volume may have altered the relative contributions of the rib cage and diaphragm to lung expansion, such that these became more equal (Grimby 1975). Drummond (1989) has shown that the rib cage - diaphragm contributions to lung inflation are inverted when spontaneously breathing anaesthetised individuals are paralysed and ventilated. If this does account for the improvement in Crs during HV ventilation, what mechanism causes reinflated areas to remain so during the extended expirations following airway occlusion during CrsHV measurements? The evidence would suggest that either airway opening was occurring with each and every subsequent reinflation, following airway occlusion, or that airway closure required longer than 2 to 3 seconds to take place.

The rapid reversal of the improvement in Crs, as demonstrated by infants 61 and 62 (Section 3.2) when low volume ventilation was re-established, suggests that the former explanation was the more probable. However, the absence of alinearity of the V - P data at lower occluded lung volumes suggests that any such airway closure, if present at all, was not occurring until lung volume had fallen below the lowest volume occlusions, such that the linear volume - pressure relationship was preserved.

It is possible that high volume ventilation decreased thoracic blood volume, reducing the splinting effect of venous congestion on lung tissue by improving pulmonary venous return. This in turn would result in an increase in lung, and therefore total, compliance. Such a scenario may explain, in part, the relationship between Crs and tidal volume during anaesthesia paralysis, with repeated high volume inflations reducing then preventing pulmonary venous congestion. With the cessation of such ventilation, and return to low tidal volumes, venous return would no longer be so assisted, this being reflected in
the reduction in Crs, as seen in the four infants in whom CrsLV could be remeasured following CrsHV (Section 3.2). However, since there continues to be considerable debate as to the true nature of the changes in thoracic blood volume during anaesthesia and anaesthesia paralysis (Nunn 1990), such an explanation, although potentially important, remains pure conjecture. In addition, in the non-anaesthetised patient, venous return is more likely to be impeded than assisted by high intrathoracic pressures. This may not be the case where thoracic blood volume (and hence circulation) have been altered by anaesthesia.

Had they been possible, concurrent measurements of absolute lung volume during Crs measurements may have helped to clarify the relationship between the two. However, such measurements were not possible at the time of the study, due to the problems of air leaks around uncuffed tracheal tubes, and the influence of halothane on gas analysers (particularly helium). In the best possible situation, with no leaks present, the additional time required to take repeat measurements of lung volume besides the Crs measurements would have unacceptably extended the duration of anaesthesia. Similar restrictions applied when measuring sedated infants pre-operatively. Measurements had to be completed during the short periods of quiet sleep between sedation and induction of anaesthesia. Such periods were frequently foreshortened by the fasted infants' hunger.

**Post-operative effects of anaesthesia**

The effects of anaesthesia on FRC and Crs are well documented, although the cause of these effects remains uncertain.

Both atelectasis and impaired gas exchange have been shown to persist during the post operative period (Jones 1990, Strandberg 1986). The persistence of atelectic areas in the lung may contribute to the significant decrease in mean oxygen saturation found post operatively in infants and children following minor surgery (Motoyama 1986). Post operative lung function has received little attention in children, except as a measure of the outcome of surgical intervention, notably for congenital heart disease (Howlett 1972).

The effect of low volume ventilation during anaesthesia on post operative respiratory mechanics, in infants and children with otherwise normal lungs, requires further study. To provide the most appropriate ventilation during anaesthesia, the long term effects of such ventilation must be studied.

The decision to use spontaneous or assisted ventilation during anaesthesia depends on a number of factors. Hulse (1984) suggests that IPPV may be
beneficial in infants due to the decrease in wasted ventilation compared with that during spontaneous breathing. In addition, the limited reserve of diaphragm function in young infants may predispose them to fatigue in the presence of an increase in the work of breathing (Keens 1978, Heldt 1987). For such infants, assisted ventilation may be essential.

The post operative complications of hypoxaemia in infants and children (Motoyama 1986), and apnoea and airway obstruction in former premature infants (Kurth 1991) may be due in part to disturbances in lung function. Although the decision to use assisted ventilation is dictated by surgical and anaesthetic considerations, the form such ventilation should take remains unclear. There is a suggestion that ventilation with low tidal volumes and PEEP may be less deleterious than high tidal volumes (and therefore high inflation pressures) with no PEEP (Quan 1990). However the post operative implications of these two methods of ventilation are unknown.
Summary

In summary

1 FRC is reduced during anaesthesia due to a combination of changes in chest wall tone, displacement of the diaphragm, and possible alterations in thoracic blood volume.

2 In the present study, it has been shown that Crs is reduced in the anaesthetised infant, with respect to the same infant during sedated sleep. By paralysing and ventilating the infant with tidal volumes approximating those measured during sedated sleep, Crs can be increased to its pre-anaesthetic value.

3 The reduction in Crs during anaesthesia appears to be due to a combination of factors, which are closely related to the changes in FRC.

4 During anaesthesia the function of the rib cage is altered as are the relative contributions made to ventilation of the rib cage and diaphragm. In the ventilated, anaesthetised, paralysed patient, ribcage excursion becomes greater than that of the diaphragm, and the complete block of tone does not add further to the fall in FRC.

5 Thoraco-abdominal blood volume changes which may occur during anaesthesia remain undefined in adults, with both increases and decreases in thoracic blood volume being described. Any such changes have yet to be examined in infants and children. The role of pulmonary venous return in altering pulmonary mechanics during anaesthesia is also unknown.

6 Changes in lung surface tension due to changes in surfactant quality or quantity may also contribute to the reduction in Crs.

7 Areas of atelectasis, which form in dependent regions of the lung in the supine anaesthetised patient, are also closely associated with the measured values of Crs in such patients.

The ability to reduce these areas of atelectasis with PEEP suggests they may play an important role in the changes in Crs reported in this thesis (Section 3), where Crs increased with more vigorous lung inflation.

8 Although atelectasis and low oxygen saturations are known to persist into the post operative period, the influence of intra-operative ventilation on post operative recovery remains unknown.
Section 5.5

Implications for clinical practice.
The adult response as a model for the infant - implications for the anaesthetised patient.

In the adult, anaesthesia results in a decrease in lung volume, chest wall tone is reduced, and the function of the diaphragm altered. Compared with the adult, the infant patient has a lung volume nearer to residual volume (i.e. has less reserve), a markedly more compliant chest wall, and a diaphragm both in a less advantageous anatomical configuration for efficient ventilation, and with fewer oxidative fibres, resulting in more rapid fatigue (Keens 1978, Openshaw 1984).

Adding the insult of anaesthesia to these disadvantages places the infant at a far greater risk of respiratory insufficiency than the adult.

When an infant is challenged with CO$_2$, the rib cage contribution to ventilation has been shown to increase. This is thought to preserve the diaphragm in its most efficient configuration. Any change in the configuration of the diaphragm during anaesthesia, as has been shown to occur in adults (Hedenstierna 1985b, Krayer 1989), may also result in a decrease in its efficiency.

The use of paralysis and IPPV in the anaesthetised adult appear to improve the uniformity of lung inflation, and this probably also applies to the infant patient (Drummond 1989, Grimby 1975).

The use of such mechanical ventilation prevents ventilatory fatigue resulting from the increased work of breathing due to anaesthesia. However, the high impedance to ventilation in anaesthetised infants, resulting from the decrease in compliance and increase in resistance, may predispose to under ventilation if pressure, rather than volume, controlled ventilation is used. This is substantiated by the marked increase in Crs which occurs when the tidal volume used for ventilation is increased. However, pressure controlled ventilation may be preferred for small infants as small leaks around the tracheal tube can be compensated for more effectively.

There is little evidence in the literature to suggest that general anaesthesia with spontaneous breathing is necessarily harmful to infants with normal cardio respiratory function, despite the underlying changes which might otherwise be expected to result in under ventilation.

By using adequate local anaesthesia, the required concentration of inhalation anaesthesia can be reduced, and this in turn minimises the risk of alveolar
hypoventilation during spontaneous breathing (Hatch 1984). Permitting an infant to breath spontaneously in this fashion prevents the problems which could occur during IPPV, especially in less experienced hands. However, extensive studies into ventilation and gas exchange have shown that, when mechanically ventilated with tidal volumes of approximately 9 ml per kg body weight, the anaesthetised infant may not only have more uniformly inflated lungs, but also have less wasted (dead space) ventilation than when breathing spontaneously (Hulse 1984). Since the stimulus of surgery and surgical manipulation may influence respiratory parameters, the evaluation of intra and post operative respiratory function must include control (or correction) for such confounding factors, as was the case in the studies quoted here. In adults, in whom more invasive measurements are possible, it has been shown that the respiratory gas imbalance which occurs with anaesthesia, can be improved, but not completely resolved, by the application of PEEP and mechanical ventilation (Tokics 1987). Unless changes in uniformity of distribution of inspired gas are matched by changes in perfusion of the lungs, impaired gas exchange will result. If one assumes that the infant lung behaves in a similar fashion to that of the adult, when atelectic areas are reinflated by IPPV or PEEP, does the pattern of improvement also follow that seen in adult patients? The greater degree of improvement in Crs seen in infants when ventilated with large tidal volumes (8-20 ml per kg) may suggest a correspondingly greater degree of reinflation. To understand, and utilise appropriately, assisted or mechanical ventilation in the anaesthetised infant, further investigation is required into the true nature of the response to both IPPV and PEEP.

Crs and the patient requiring assisted or mechanical ventilation. Increasingly, measurements of Crs are being used to monitor the respiratory status of the ventilated infant and neonate, particularly when assessing the response to treatment or clinical intervention (Seidenberg 1989, Dreizzen 1989, Brundage 1990, Balsan 1990).

It has been demonstrated in infants, as in adults, that increasing inspiratory volume (tidal volume), or lung volume (FRC, by applying PEEP) may result in a reduction in Crs in the patient with lung disease (Suter 1973, Katz 1981). This has been attributed to an over expansion of portions of the lung, such that ventilation is occurring at the upper portion of the V - P curve of the
respiratory system. Greater pressures are required to inflate the overstretched lung tissue and chest wall, which at these volumes will be tending to recoil inwards rather than outwards as is normally the case during tidal ventilation.

This, and the marked volume dependency of Crs in the anaesthetised infant demonstrated in this thesis (Section 3.2), suggest the following:-

1. The inter dependence between measured values for Crs, and the mode and pattern of ventilation at the time of measurement, have important implications when monitoring mechanics in the infant receiving assisted ventilation.

Any changes to ventilation need to be documented and accounted for when assessing the results of such measurements.

2. When the response to changes in ventilation is required, a simple measure of Crs may provide adequate information about the infant's current status and assist in assessing whether the changes were appropriate.

3. To monitor changes over a period of time, closer attention needs to be paid to factors such as tidal volume, frequency and PEEP which, if altered, may influence the measurements. The most useful longitudinal measurements are those accompanied by simultaneous measurements of absolute lung volume. A complete picture of the V - P characteristics of the respiratory system can then be formed and, allowing for changes in lung volume, changes in Crs assessed more accurately in terms of disease status.
Summary of research, future directions

The multiple occlusion technique

1. The multiple occlusion technique has been applied successfully to measure Crs in sedated, anaesthetised and anaesthetised paralysed infants.

2. Active expiratory effort was a greater problem during measurements in the anaesthetised infant than in the sedated infant. This makes the MOT (and PFVT and MIT) unsuitable for routine use in spontaneously breathing anaesthetised infants.

3. The MOT compared favourably with the PFVT, which was found to have a higher failure rate when used in sedated infants.

4. The MIT, an adaption of the MOT, could decrease the time required for data collection and improve the quality of data in the presence of an unstable end expiratory level.

5. Crs was measured using the MOT in infants with a wide variety of respiratory disorders, including the need for assisted ventilation. Such measurements can assist in the diagnosis and monitoring of disease processes. Concurrent measurements of lung volume are important for an informed interpretation of the results.

6. Computerising data collection and analysis (Appendix A1) for the MOT permits unbiased re-examination of the raw data, including multiple plots of the various signals. Data collection and analysis have been simplified, and storage requirements reduced.
**Anaesthesia**

1. Following induction of halothane anaesthesia Crs was reduced by approximately 35%, similar to the response previously reported in adults.

2. During anaesthesia paralysis, Crs demonstrated a marked dependence on the tidal volume being administered during measurements. This may in part explain the discrepancies between earlier reports of compliance measurements in anaesthetised paralysed infants. By ventilating the infant with tidal volumes approximating those measured during sedated sleep, Crs could be increased to its pre-anaesthetic value.

From the work of other authors:-

3. The reduction in Crs resulting from the induction of anaesthesia is closely related to the concurrent reduction in FRC.

4. The reduction in FRC (and Crs) may be due to a combination of changes in chest wall tone, displacement of the diaphragm, and possible alterations in thoracic blood volume.

5. In addition Crs may be altered during anaesthesia by abnormal pulmonary venous return, and changes in surfactant quality or quantity.

6. Areas of atelectasis which form in dependent regions of the lung in anaesthetised patients can be reduced by applying PEEP. This may contribute to the increase in Crs resulting from more vigorous lung inflation in paralysed infants (CrsHV).

7. Atelectasis and low oxygen saturations are known to persist into the post operative period, yet the influence of intra-operative ventilation on post operative recovery remains unknown.
Further Research

Anaesthesia

Changes in the elastic properties of the respiratory system resulting from anaesthesia require further study. A clear picture of the sequence and magnitude of events has yet to be constructed.

Clarification is needed of the nature of the thoraco-abdominal blood volume changes and the altered function of the diaphragm during anaesthesia, particularly as this relates to infants and children.

The ethical and behavioural problems of making the necessary measurements in children cannot be underestimated. The increasing availability of less invasive imaging techniques, frequently requiring light anaesthesia to obtain CO₂ operation, may provide the means to study these elusive parameters in children.

To explain both the reduction in Crs during anaesthesia, and the changes in Crs with changes in tidal volume, there are two areas of particular importance:

1. the nature, role and response to anaesthesia of surfactant, and
2. the nature of pulmonary venous return during anaesthesia and anaesthesia paralysis.

This pertains particularly to anaesthesia, but may have important implications for the non-anaesthetised infant requiring assisted ventilation.

The postoperative influences of the type of ventilation received during anaesthesia are largely unknown. To minimise the adverse effects of anaesthesia, controlled studies are needed to assess the medium and long term effects of the different methods of ventilation on respiratory function and gas exchange.

Comparative studies between the use of IPPV with or without PEEP in anaesthetised infants are needed to assess the influence of each on atelectasis (lung expansion or re-expansion), respiratory mechanics and gas exchange, both intra- and post-operatively. A similar profile is required of the effects of using PEEP with spontaneous breathing, to ascertain the optimum ventilation for the small young patient during anaesthesia.
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Appendix A1

Computerisation of data collection and analysis

Introduction
With the evolution of methods of measuring respiratory mechanics during tidal breathing in children, and the increasing need to be able to review data repeatedly in its original form, computerised digital recording was seen to have the potential to overcome several important disadvantages inherent in paper and / or tape recordings:
1. Once paper copy has been marked for analysis it cannot be re-examined without bias at a later date.
2. Magnetic tape recordings allow data replay through oscilloscope or paper recorder, but not without some loss in quality of the signals.
3. Analogue integration of a flow signal to obtain volume is notorious for drift in the resulting volume signal. Although this can be minimised, it is very difficult to eliminate totally, and cannot subsequently be corrected. When constructing volume-flow loops for Passive Flow Volume (PFV) measurement of Rrs or Crs, volume drift can result in inaccurate results.
4. Many of the recently developed methods of measuring respiratory mechanics in infants, such as the passive flow volume (PFV) and partial forced expiratory flow volume (PEFV) methods, require analysis of flow -volume curves. Historically this has resulted in data being collected onto magnetic tape and later replayed more slowly through X-Y plotters, the latter usually having too slow a response time for use during data collection. By recording data in digital form, initially onto a computer hard disk (with backups on floppy disks), repeated recall of the original data, as it was recorded at the time of study, became feasible.
Such data is not subject to deterioration, and can be analysed repeatedly. In addition, as analysis files can be stored independently from the original data files, observer bias can be eliminated.
The recalled data can be manipulated in terms of definition (size) of display, plot form, and hard copy (printer or plotter) in a manner and with an ease which it is difficult to achieve with analogue signals without very expensive hardware.
Digital integration of the flow signal can be used to overcome any problem of electronic integration drift, stabilising the volume signal during recordings and improving the accuracy of measurements taken from flow volume plots for the PFV and PEFV techniques.
With improved access to re-examine recorded data, it is possible to examine inter observer differences in data analysis and interpretation without bias resulting from another person's markings on the recordings. As signals can be recorded in their calibrated state, data analysis is simplified, any appropriate statistical calculations being undertaken automatically by the computer.

For data collection using a digital system, software can be written to enable the incoming data channels to be displayed with respect to time or each other. Similarly, retrospective recall and plotting of data is more immediate (and ready calibrated) compared with searching for, calibrating, and analysing, data from magnetic tape recordings.

With the increasing cost of high quality paper for analogue recorders, storing data on computer floppy disks represents a significant reduction in cost both financially and in terms of storage space. The approximate comparative costs of storing data, to an equivalent quality when examined after collection, was £15 paper to £0.80 floppy disks.
A1.1 Equipment
To run the RASP software (Physio Logic Ltd) for data collection and analysis, the following were installed:
Zenith (IBM compatible) AT computer with
40 Mbyte hard disk Clock speed 12 MHz 512 kbytes RAM
Data Translation A-D extension board
2 1.2 Mbyte 5¼" Floppy disk drives (later systems having one 3½" and one 5¼" floppy disk drives)
VGA colour monitor
Epson LX50 dot matrix printer
Microsoft mouse - added subsequent to installation of the computer
80287 Math Co-processor fitted later
RASP Users Guide (Physio Logic Ltd)

Signal inputs
Airway pressure and flow signals from the Validyne transducers were fed into a double output junction box. One output was fed directly onto the A-D card, the other output supplied the analogue system as described previously (Fig A.1).
Sampling frequency was initially set at 40 Hz, dictated by hardware and software limitations. As these problems were overcome, sampling frequency could be varied between 1 and 400 Hz. The flow input was digitally integrated to give volume. Collecting these 4 signals, time, flow, airway pressure, and tidal volume, at a sampling frequency of 40 Hz, the memory buffer collected 45s of data before beginning to over-write from the beginning. Each buffer of data when saved to disk constituted a saveset and a predetermined number of savesets a file. New files were automatically opened as the previous one reached capacity.
The number of savesets per file was set to ensure the final file size was no greater than could be accommodated on a high density 5¼" floppy disk, i.e. 1.2 Mbytes.
Figure A.1  Analogue and digital recording systems in tandem. Analogue signals taken from validyne amplifiers and directed to both Ultra Violet light recorder and A to D card of computer.

Figure A.2  On-screen display of flow (upper), volume (middle) and pressure at the airway opening (lower) signals during data collection.
A1.2 Program requirements

1. Volume signal
Volume signal by digital integration was the most significant improvement expected as compared with the analogue system.

2. Calibration
All signal inputs were recorded in the calibrated state, zero flow being the most important calibration point.
A two point calibration was used to calculate a linear transform between the incoming electrical signal and the corresponding physical displacement applied to the transducer. The effective range of the input signal and the minimum detectable change (one step of the A to D converter) were displayed. The Validyne amplifier was adjusted to maintain the flow range (+10v) just within the range of linearity of the pneumotachograph to ensure the greatest sensitivity of signals, i.e. each step of the A to D converter represented as small a change as possible in the physical signal.
Due to the constraints of time when taking sequential measurements on the same child in the ward and then in the anaesthetic room, it was necessary to have a facility for retrospective calibration of recorded data. This was required because of characteristics of the different gases used in the two environments, air in the ward and nitrous oxide/oxygen in the anaesthetic room.
Signals of a known magnitude could be recorded at the time of study (after data collection if necessary) and used later to apply a corrected calibration factor and offset to the data.

Data collection
To enable time based display of signals to be used for the timing of airway occlusions during expiration, there was minimal delay (0.025s) between signal generation and on screen display (Fig A.2).
Although sampling rate was initially set to 40 Hz, later versions of RASP enabled this to be varied between 1 and 400 Hz. As sampling rate increased, there was corresponding decrease in the length of time a full buffer represented. Thus for the MOT, data collection at 40 Hz gave adequate signals for detailed analysis but allowed maximum time per saveset. Sampling rates of the order of 400 Hz were required when checking the response characteristics of the equipment.
With increasing familiarity with the computerised system, sampling rates were tailored more to the respiratory pattern of the child being measured.
Data from children whose respiratory rates were greater than approximately 40 breaths per minute were difficult to interpret if sampling was as low as 40 Hz. In such children sampling at 100 Hz was required to provide adequately detailed data for analysis. Much of this detail would have escaped attention on paper recordings.

To enable a single operator to collect data during studies on non-anaesthetised patients, digital foot switch control was introduced. Data could be automatically saved and stored to hard disk, or stored following the addition of a comment pertinent to the data. Automatic saving could be operated either using either the foot switch or the keyboard.

Analysis
Operator input was maintained, with limited automation of the analysis procedure.

Volume baseline
End expiratory volume baseline was determined by either fitting a line to pre determined volume minima, as calculated by applying least squares linear regression analysis to the minima values (Fig A.3), or taken as a spot value, determined by positioning a cursor on the chosen minimum volume (Fig A.4).

Providing any volume drift had been eliminated, the latter method was that of choice both for stable and unstable end expiratory levels (Fig A.4).

Equilibrated airway (plateau) pressure during occlusion, δP
Initially taken as a spot value determined by cursor placement (cursor B in Fig A.3), this was later adapted to mean the sample values over a stated period of the pressure plateau, 0.1 or 0.2 seconds depending on the respiratory rate of the child. This minimised intra and inter observer variability, particularly where cardiac artifact was visible as signal noise on the P recording.

Results
Analysis tables displayed both the measured and derived parameters (Table A.1), with mean and standard deviations calculated for each column. X-Y scatter plots could be constructed from any combination of these parameters.
Multiple occlusion technique (Page 1 of 4):

SD Pao plateau  0.007kPa  Mn Pao plateau  0.915kPa
Ut  46.98ml  Occluded volume  44.55ml
Mn Respiratory Rate  49.6/min  Vocc/Pao plateau  48.71ml/kPa

Figure A.3  End expiratory level calculated by linear regression through pre-determined number of volume minima.

Multiple occlusion technique (Page 1 of 4):

SD Pao plateau  0.009kPa  Mn Pao plateau  0.753kPa
Ut  94.95ml  Occluded volume  83.18ml
Mn Respiratory Rate  29.7/min  Vocc/Pao plateau  110.53ml/kPa

Figure A.4  End expiratory level determined by the position of cursor A on a chosen volume minimum.
For the compliance measurements, the occluded volume vs airway plateau pressure (V-P data) of analysed occlusions was displayed, with the slope obtained by least squares regression analysis of the data superimposed. All sets of analyses were saved as discrete files but with the facility to recall the original time based data and display it as analysed, subject to the data files being available to the computer.

Hard copy of the analysis tables and plots were obtained on completion of an analysis (Table A.2).

Analysis sequence:

The end expiratory level and Pao plateau values were determined by the operator (Fig A.5). Before accepting data from an occlusion, the applied end expiratory level and Pao plateau were examined to ensure both had been appropriately marked.

These data, once accepted, were stored and could be viewed both in a display table (Table A.2) and in the form of a Volume - Pressure plot with the statistics displayed for the slope, including the 95% confidence interval for the slope and its intercept on the volume axis.
Multiple occlusion technique (Page 1 of 4):

SD Pao plateau 8.66kPa

Vs 49.43ml

Mn Pao plateau 8.65kPa

Occluded volume 26.00ml

Mn Respiratory Rate 49.5/min

Uocc/Pao plateau 42.60ml/kPa

Figure A.5 Crs analysis using RASP software. Screen image following marking of an occlusion. Cursor A determines end expiratory level (to predetermined strategy), cursor B marks start of pressure plateau (see text).

Table A.1 Display table of results from Crs analysis using RASP software.

<table>
<thead>
<tr>
<th>#</th>
<th>RR /min</th>
<th>Tpao plat s</th>
<th>Pao plat kPa</th>
<th>SD kPa</th>
<th>Pao plat kPa</th>
<th>Vocc ml</th>
<th>Uocc/Pao plat kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>46.6</td>
<td>0.20</td>
<td>0.961</td>
<td>0.561</td>
<td>47.28</td>
<td>49.21</td>
<td></td>
</tr>
<tr>
<td>2.01</td>
<td>50.7</td>
<td>0.20</td>
<td>0.843</td>
<td>0.343</td>
<td>45.23</td>
<td>49.38</td>
<td></td>
</tr>
<tr>
<td>3.01</td>
<td>54.9</td>
<td>0.20</td>
<td>8.916</td>
<td>4.516</td>
<td>49.38</td>
<td>49.38</td>
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</tr>
<tr>
<td>4.01</td>
<td>57.5</td>
<td>0.20</td>
<td>0.843</td>
<td>0.343</td>
<td>42.41</td>
<td>58.20</td>
<td></td>
</tr>
<tr>
<td>5.01</td>
<td>63.8</td>
<td>0.20</td>
<td>0.961</td>
<td>0.561</td>
<td>44.29</td>
<td>49.57</td>
<td></td>
</tr>
<tr>
<td>6.01</td>
<td>51.6</td>
<td>0.20</td>
<td>0.821</td>
<td>0.421</td>
<td>40.69</td>
<td>49.57</td>
<td></td>
</tr>
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<td>51.05</td>
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<tr>
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<td>0.20</td>
<td>0.821</td>
<td>0.421</td>
<td>43.79</td>
<td>50.23</td>
<td></td>
</tr>
</tbody>
</table>

Mean: 55.9 | 0.20 | 0.844 | 0.564 | 37.26 | 46.96 |

SD: 5.0 | 0.08 | 0.182 | 0.137 | 0.86 | 3.00 |

Display: ↓↑1.4 Files Tag Use (Alt-S/T/X) F0 summary F2 menu ↑
Table A.2  Report table of results from Crs analysis using RASP software

Multiple occlusion technique

Subject: SAM
Note:
Analysis File: SAM.M01
Remark:

<table>
<thead>
<tr>
<th>#</th>
<th>Filename/Saveset</th>
<th>Note</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>2.01</td>
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<td>88112101.CAL/</td>
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</tr>
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<td>7</td>
</tr>
<tr>
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<td>7</td>
</tr>
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<td>88112101.CAL/</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>RR/min</th>
<th>TPao plat</th>
<th>Pao pl SD</th>
<th>Pao plat</th>
<th>Vocc</th>
<th>Vocc/Paopl</th>
</tr>
</thead>
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<td>49.38</td>
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<td>0.648</td>
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<td>0.009</td>
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<td>0.20</td>
<td>0.009</td>
<td>0.893</td>
<td>44.29</td>
<td>49.57</td>
</tr>
<tr>
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<td>61.6</td>
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<td>0.872</td>
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<td>50.23</td>
</tr>
</tbody>
</table>

Mean RR: 55.9
Mean TPao plat: 1.00
Mean Pao pl: 0.20
SD RR: 5.8
SD TPao plat: 0.00
SD Pao pl: 0.00

Mean Vocc = 37.26 ml
Mean Vocc/Paopl = 46.98 ml/kPa
Mean Slope = 63.747 ml/kPa
Mean Y'cept = -12.73 ml
Mean X'cept = 0.289 kPa
Mean Corr. = 0.9728

V - P data from above report
A1.3 Assessment of the computer system

Data collection
To allow an objective comparison to be made between data collected using the analogue system and that collected directly on to the computer hard disk, initial measurements on children were made using the two systems simultaneously (Fig A.1). This also ensured that no infant measurements were lost due to the lack of familiarity with the computer data collecting system. Initially, calibration of the flow input was difficult, especially in the anaesthetic room where space and time were very limited. The computer program forced far greater care and accuracy of calibration than paper recording. On paper, a known signal was recorded and used to obtain a calibration factor for that signal. Any inconsistency between, for example, a flow signal and its derived volume signal were simply not apparent. Inaccurate calibration of the flow signal when using the computer was revealed immediately a known volume was applied, with the resulting integrated volume being smaller or greater than the given signal. Offset flow zero was manifested as a volume drift as soon as integration commenced.

Immediate advantages and disadvantages.

Volume drift
When there was volume drift due to an offset on zero flow, it was not necessary to interrupt data collection to retrieve the volume signal. Once the extent of the drift was known RASP could calculate a correction factor, thus stabilising the volume signal display for subsequent recording. Data could be collected, checked and accepted or discarded as appropriate. Being able to discard data where, for example, there was a face mask leak, reduced the quantity of collected data and also saved time when seeking that which was suitable for analysis. Although each saveset of data only covered a short time period of the measurement when compared with a more continuous paper trace, any particular part of the measurement could be instantly recalled for review. This made it possible to monitor the quality and quantity of data collected during a measurement. With the UV paper recordings, repeated exposure to light caused the signals to deteriorate, and for this reason and to protect the paper from damage, the paper was rolled as it accumulated after recording. To examine earlier recordings on such a trace was both awkward and time consuming when time was most critical.
Data analysis
The analysis of V - P data for MOT was checked in two ways. To ensure data handling by the computer program was accurate and correct, the actual calculations made by the program were checked with reference to the data sample values, i.e. the actual values as recorded during measurement.

A full record was printed of every sample for flow, volume (integrated flow), and airway pressure, recorded during a measurement of Crs. Using these data, the strategies and algorithms being used by RASP to calculate Crs were checked to ensure that appropriate samples were being used (such as when determining end expiratory level), and that derived parameters (such as Crs, respiratory rate, tidal volume) were being correctly calculated. This ensured both the strategies were appropriate, and algorithms included correct formulae.

See Appendix A - RASP Multiple Occlusion Technique Validation, for detailed description.

Comparison of analyses
To be confident that the computer analysis referred to the same parameters as those previously determined from paper recordings, analyses from the two data types were compared. This was important if newly acquired data were to be compared or combined with data based on earlier paper recordings.

In 6 children data were compared for a total of 14 measurements representing the sedated, anaesthetised, and anaesthetised paralysed states.

Results
Table A.3 summarises the children's details and results of analyses. Where occlusions were recorded only on one medium, paper or computer, these were omitted from comparison analyses (see above). Thus data presented here are from matched occlusions only.

The average difference between the paper and computer analysis was -1.68 ml.kPa⁻¹ (SD 2.95) or -3.88% (± 4.50%).

There were several satisfactory occlusions recorded on computer which could not be analysed on paper trace due to volume drifting above the margin of the paper. The galvanometer system of light deflection of the UV recorder allowed unrestricted travel of the beams. Thus there was no warning of signals moving outside the range of the paper. To control for this, prior to using the computer, the Tektronic oscilloscope and UV recorder signals were matched such that loss of a signal from the screen implied loss of signal.
from the paper recording (see section 2.2).

With the more stable volume displayed on the computer screen being available to time occlusions, the volume signal drift from the analogue integrator was less easily observed, with the consequent loss of some occlusions from the paper recording.

Data retrieved from disk could frequently be examined more closely than that on the paper trace. The slower paper speed set for sedated breathing prior to the measurements during anaesthesia was sometimes inadequate for data collection during halothane anaesthesia when respiratory rate commonly increased. In addition, in intubated infants, cardiac activity was occurring in such close proximity to the tracheal tube that a cardiac pressure wave was seen frequently, superimposed upon the airway pressure and flow traces. This cardiac artifact combined with rapid respiratory rates tended to obscure the detail of P plateaus, especially at low occluded volumes.

In contrast, the computer signal of the same plateau could be expanded on the time axis to the limit set by the original sampling frequency at the time of data collection. This was never less than 40 Hz and therefore resulted in definition equivalent to running paper at 2 cm.s\(^{-1}\).

As signals on the computer could be enlarged vertically, assessment of the low volume, and thus low pressure, occlusions was based on a greater knowledge of the signal quality of the occlusion itself, than was possible for similar data on the paper recording.

The one appreciable problem in analysing data on the computer was the loss of a continuous time based recording of the volume trace over a period of many seconds or a few minutes. Savesets of data approximately 45 seconds long gave less information with respect to end expiratory level than a continuous paper recording of several minutes.

This initially resulted in increased scatter of the V-P data as factors influencing EEL, such as sighs, short respiratory pauses or apnoeas, were not always evident from the computer recording. Similarly, because of the limited data collected following an occlusion, it was less easy to differentiate small leaks, around the facemask or tracheal tube, from unstable end expiratory levels.

The true magnitude of the cardiac artifact visible on the Pao trace on the computer display during airway occlusion, revealed the extent of the 'smoothing - by - eye ' which occurred during analysis of paper recordings. It was this variability in Pao over very few samples which led in turn to Pao pressure during an occlusion being taken as the mean value over 0.1 to 0.2 s,
Table A.3
Comparison between paper and computer analysis of V - P data for Crs

<table>
<thead>
<tr>
<th>Infant No</th>
<th>State</th>
<th>Crs (ml.kPa⁻¹)</th>
<th>95% CI Int</th>
<th>R²</th>
<th>Crs (ml.kPa⁻¹)</th>
<th>95% CI Int</th>
<th>R''</th>
<th>% difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>S</td>
<td>102</td>
<td>88 - 117</td>
<td>-8.0</td>
<td>0.96</td>
<td>107</td>
<td>91 - 122</td>
<td>-8.9</td>
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<tr>
<td>SW</td>
<td>S</td>
<td>27</td>
<td>23 - 33</td>
<td>-6.2</td>
<td>0.96</td>
<td>27</td>
<td>21 - 35</td>
<td>-6.4</td>
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<tr>
<td>76</td>
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<td>77</td>
<td>66 - 89</td>
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<td>0.95</td>
<td>78</td>
<td>57 - 89</td>
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<td>A</td>
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<td>17</td>
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<td>0.86</td>
<td>27</td>
<td>10 - 46</td>
<td>-10.9</td>
<td>0.70</td>
</tr>
<tr>
<td>P</td>
<td>65</td>
<td>28</td>
<td>101 - 12.5</td>
<td>0.90</td>
<td>60</td>
<td>16 - 103</td>
<td>17.5</td>
<td>0.87</td>
</tr>
<tr>
<td>78</td>
<td>S</td>
<td>188</td>
<td>171 - 207</td>
<td>12.4</td>
<td>0.97</td>
<td>183</td>
<td>160 - 208</td>
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</tr>
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<td>A</td>
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<td>64</td>
<td>131 - 1.4</td>
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<td>95</td>
<td>64 - 125</td>
<td>+0.9</td>
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</tr>
<tr>
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<td>189 - 13.3</td>
<td>0.90</td>
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<td>162 - 179</td>
<td>18.9</td>
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<td>126</td>
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</tr>
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<td>0.97</td>
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<td>0.97</td>
</tr>
<tr>
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<td>40</td>
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<td>0.98</td>
<td>36</td>
<td>33 - 38</td>
<td>2.8</td>
<td>0.98</td>
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</table>

Footnote
Infants 76 (A), 80 (A) and 82 (S) have poor correlation coefficients as this analysis was limited to matched occlusions only (see text). Unusable as measurements of Crs, these results have been quoted here to demonstrate the close matching of results from both good and poor set of data. These results may therefore differ from those in Section 3, where additional occlusions may have been available on paper recordings, and where only data meeting the regression criteria described in Section 2 are included.

Legend
State: S sedated; A anaesthetised; P anaesthetised - paralysed
Intercept: Volume intercept on extrapolation of V - P data.

Mean: -3.9
SD: ±4.5
A1.4 Discussion

The scope for rapid signal manipulation has enabled significant advances in both equipment assessment and data collection and analysis. Data collection and storage were significantly simplified with less data lost through drift of signal off the trace, or poor signal quality, as compared with paper recordings. Savings were also made in terms of the cost and space required for data storage. The advanced programming of the software allowed the immediate creation of X - Y plots of any chosen signals, and scatter plots of analysed parameters. Although for Crs measurement, requirements were limited to V - P plots and time based display of recorded signals, this facility enabled detailed examination of tidal and occluded breathing. This was particularly important when studying the mechanics of infants with abnormal lung function, when the shape of the flow - volume loop may be as informative as the airway occlusion measurements (Manual of Infant Lung Function Testing, Dezateux 1991). All data could be reanalysed without influence from previous analyses, important both for checking inter and intra observer variability, and as a teaching aid.

**Speed and accuracy.**

Data collection did not depend on critical matching of signals between the display and recording apparatus, since both facilities had a common source. The calibration of signals was found to require much greater attention, as an inaccurate flow calibration resulted in an inaccurate volume signal. This resulted in more reproducible calibration, as indicated by the stable calibration factor for the flow input on the computer compared with those derived from the paper traces. Data analysis was faster, particularly as all mathematical/statistical procedures occurred automatically, saving time and reducing the risk of errors in data entry.

**Flexibility**

An important advantage the RASP system had over other commercially available systems, was that it could be used immediately with the existing hardware. No modifications to RASP were required to allow for variables such as different size (and thus sensitivity and range) of pneumotachograph. From the data analysis checks, it was clear that results of measurements obtained using the computer for data collection and analysis could be used interchangeably with those obtained previously using paper recordings.
Teaching

The ability to retrieve clean (unmarked) data and control the number of channels appearing on the screen at any one time contributed to making the system an excellent teaching tool. This applied both for basic physiology, with respiratory parameters appearing in real time, and when training individuals in infant lung function measurement.

With the signals appearing in their calibrated form, during measurements on anaesthetised infants and young children the absolute inflation pressures and tidal volumes could be seen on the screen display. These parameters are rarely monitored during manual ventilation of the anaesthetised child, most anaesthetists being unaware of the magnitude, particularly of pressure, of their manual inflations (ongoing research within this Laboratory).

Extraneous use

An unexpected bonus of participating in the development of this software has been the creation, in effect, of a small mobile laboratory. By calibrating the flow and pressure inputs the system could be used to measure these parameters in any setting. This proved particularly useful when assessing the flow-volume characteristics, and resistance to airflow, of any apparatus. These included ventilator circuits, measurement apparatus, and other breathing circuits (Hatch 1990, Dezateux 1991). Once calibrated, a simple recording of increasing or decreasing flow and the corresponding changes in pressure, could provide an instant plot of pressure against flow, the slope of which was resistance.

Any data manipulation not available within the RASP program could be readily achieved using any statistical package, as both the individual calibrated samples and derived parameters could be exported in ASCII format.
Developments and further applications

To overcome the problems of analysing a limited time span of data, the RASP software was updated to permit up to 163 seconds of continuous recording per saveset of data (at 50 Hz). Thus several brief airway occlusions could be performed which had a common end expiratory level, with adequate uninterrupted breathing between each to ascertain the stability of the end expiratory level. This facilitated more thorough checking for possible small leaks around face mask or tracheal tube, than had been possible with the shorter savesets.

For those studying Crs in ventilated infants receiving CPAP, the facility to correct for end expiratory airway pressure has been incorporated into the RASP software by Physio Logic.

The dual time base version of the program allows snapshots of events such as airway occlusions to be saved in context with a less detailed but continuous record of parameters over several hours. Thus both short and long term variability can be monitored, with up to 8 analogue input channels and additional derived channels, such as tidal volume, and respiratory frequency.

The RASP software has also been incorporated for data collection and analysis of infant whole-body plethysmographic measurements of thoracic gas volume (TGV) and airways resistance (Raw). In this system, the most outstanding improvement was the ability to maintain the notoriously unstable signal, plethysmograph pressure, within the limits of recording on the computer more easily than when trying to achieve the same sensitivity on the paper trace.

With the facility to export data in ASCII form, it is possible to import these data files into Programs such as SAS for more detailed statistical analysis such as multiple regressions, and calculating best-fit curves.

This facility could be exploited extensively to assist in complex modelling of the behaviour of the respiratory system, an area of growing international interest.

The RASP software has a place at the centre of research recordings of any respiratory parameters in infants and adults, and also contributes towards a high standard of clinical measurements.

In addition, the versatility of the program makes any measurement system into which RASP has been incorporated a useful tool for the assessment of equipment characteristics (see extraneous uses, above).
A1.5 Validation of the RASP algorithms

The handling of the physical data by the RASP software was assessed in two steps, identifying sample values, and application of algorithms. Once a representative analysis had been completed, this was examined in detail as described below.

Identifying sample values

For a given marked occlusion, a printout of the absolute values for each physical channel throughout the period included in the analysis was obtained using a Report facility within RASP. Table A.5 shows a small portion of such a printout.

Using the Debug facility, for the analysis under examination a detailed breakdown of the strategies used (number of breaths, scan periods etc), samples identified, and subsequent calculations applied by RASP was obtained. The record of the raw data (table A.5) was then scrutinised to ensure that appropriate samples, listed in the Debug printout, had been identified as listed below.

Sample

A  Position of cursor A
B  Position of cursor B
C  Start of inspiration of the analysed breath
D  End of inspiration of the analysed breath
E  Peak expiratory flow, pre occlusion
F  Peak expiratory flow, post occlusion
G  End of expiration of the analysed breath, (or 1.5 'normal' breaths after sample C)
H  Start of the occlusion
I  End of the occlusion
J  (Reserved)
K  (Reserved)
L  Start of the analysed portion of the Pao plateau
M  End of the analysed portion of the Pao plateau
N  Start of inspiration of the last breath in the period of control breathing
P  End of inspiration of the last breath in the period of control breathing
Q  End of expiration of the last breath in the period of control breathing
R  Start of the period over which mean PEEP is estimated
S  End of the period over which mean PEEP is estimated

230
Application of algorithms

Using these sample values and intermediate values where appropriate, also listed in the Debug printout, analysis streams were then calculated:

Analysis Streams

Control breathing

<table>
<thead>
<tr>
<th>Stream</th>
<th>Physical channel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mean respiration rate, RR</td>
</tr>
<tr>
<td>2</td>
<td>SD of the respiration rate</td>
</tr>
<tr>
<td>3</td>
<td>Mean tidal volume, VT</td>
</tr>
<tr>
<td>4</td>
<td>SD of the tidal volume</td>
</tr>
<tr>
<td>5</td>
<td>Mean inspiratory time, TI</td>
</tr>
<tr>
<td>6</td>
<td>SD of inspiratory time</td>
</tr>
<tr>
<td>7</td>
<td>Mean expiratory time, TE</td>
</tr>
<tr>
<td>8</td>
<td>SD of expiratory time</td>
</tr>
<tr>
<td>9</td>
<td>Mean TI/Ttot</td>
</tr>
<tr>
<td>10</td>
<td>SD of TI/Ttot</td>
</tr>
<tr>
<td>11</td>
<td>Mean time to peak expiratory flow, TPEF</td>
</tr>
<tr>
<td>12</td>
<td>SD of time to peak expiratory flow</td>
</tr>
<tr>
<td>13</td>
<td>Mean TPEF/TE</td>
</tr>
<tr>
<td>14</td>
<td>SD of TPEF/TE</td>
</tr>
<tr>
<td>15</td>
<td>Mean peak expiratory flow, PEF</td>
</tr>
<tr>
<td>16</td>
<td>SD of peak expiratory flow</td>
</tr>
<tr>
<td>17</td>
<td>Mean inspired volume remaining in the lungs at the instant of PEF, VPEF</td>
</tr>
<tr>
<td>18</td>
<td>SD of inspired volume remaining in the lungs at the instant of PEF</td>
</tr>
<tr>
<td>19</td>
<td>Mean VPEF/VT</td>
</tr>
<tr>
<td>20</td>
<td>SD of VPEF/VT</td>
</tr>
<tr>
<td>21</td>
<td>Mean VT/TI</td>
</tr>
<tr>
<td>22</td>
<td>SD of VT/TI</td>
</tr>
<tr>
<td>23</td>
<td>Mean VT/TE</td>
</tr>
<tr>
<td>24</td>
<td>SD of VT/TE</td>
</tr>
</tbody>
</table>

Analysed breath

<table>
<thead>
<tr>
<th>Stream</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Tidal volume of the occluded breath, VTocc</td>
</tr>
<tr>
<td>26</td>
<td>Occluded volume, Vocc</td>
</tr>
<tr>
<td>27</td>
<td>Released volume, Vrls</td>
</tr>
<tr>
<td>28</td>
<td>Fractional occluded volume</td>
</tr>
<tr>
<td>29</td>
<td>Reserved</td>
</tr>
<tr>
<td>30</td>
<td>Duration of the analysed portion of the Pao plateau during the occlusion, Tocc</td>
</tr>
<tr>
<td>31</td>
<td>Mean value of Pao over the analysed portion of the plateau, Paoocc, relative to atmospheric pressure</td>
</tr>
<tr>
<td>32</td>
<td>SD of Pao over the analysed portion of the plateau</td>
</tr>
<tr>
<td>33</td>
<td>Spot value of the ratio of the occluded volume to Paoocc (relative to PEEP)</td>
</tr>
</tbody>
</table>
Mean positive end-expiratory pressure for ventilated subjects

Mean value of Pao over the analysed portion of the plateau relative to the mean PEEP

Intermediate calculations, such as that of end expiratory baseline which was required to calculate tidal volume, were also detailed in Debug and checked manually using an independent calculator for all statistical calculations.

Finally, the analysis streams themselves were subjected to statistical analysis to check that all derived values were correctly reported. This included least squares linear regression analysis of the V - P data (analysis streams 26 and 31) with calculation of the 95% confidence intervals for the slope and intercept.

All strategies identified samples appropriately, and both tidal breathing and occluded breath streams were correctly calculated. Statistical data derived from these streams were also correct.

Table A.5 Printout of individual sample values for physical channels flow, volume and pressure, as recorded using RASP software.

<table>
<thead>
<tr>
<th>SAMPLE #</th>
<th>Time</th>
<th>Flow</th>
<th>Vol</th>
<th>Pao</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>s</td>
<td>ml/s</td>
<td>ml</td>
<td>kPa</td>
</tr>
<tr>
<td>1</td>
<td>1.230</td>
<td>92.206</td>
<td>4.3189</td>
<td>-0.03557</td>
</tr>
<tr>
<td>2</td>
<td>1.240</td>
<td>101.690</td>
<td>5.2884</td>
<td>-0.04327</td>
</tr>
<tr>
<td>3</td>
<td>1.250</td>
<td>110.647</td>
<td>6.3501</td>
<td>-0.05097</td>
</tr>
<tr>
<td>4</td>
<td>1.260</td>
<td>119.077</td>
<td>7.4987</td>
<td>-0.05097</td>
</tr>
<tr>
<td>5</td>
<td>1.270</td>
<td>126.433</td>
<td>8.7263</td>
<td>-0.05611</td>
</tr>
<tr>
<td>6</td>
<td>1.280</td>
<td>132.249</td>
<td>10.0198</td>
<td>-0.06124</td>
</tr>
<tr>
<td>7</td>
<td>1.290</td>
<td>137.518</td>
<td>11.3687</td>
<td>-0.06638</td>
</tr>
<tr>
<td>8</td>
<td>1.300</td>
<td>142.787</td>
<td>12.7702</td>
<td>-0.06895</td>
</tr>
<tr>
<td>9</td>
<td>1.310</td>
<td>147.792</td>
<td>14.2231</td>
<td>-0.07152</td>
</tr>
<tr>
<td>10</td>
<td>1.320</td>
<td>150.690</td>
<td>15.7155</td>
<td>-0.07665</td>
</tr>
<tr>
<td>11</td>
<td>1.330</td>
<td>153.852</td>
<td>17.2382</td>
<td>-0.07665</td>
</tr>
<tr>
<td>12</td>
<td>1.340</td>
<td>157.276</td>
<td>18.7939</td>
<td>-0.08179</td>
</tr>
<tr>
<td>13</td>
<td>1.350</td>
<td>160.174</td>
<td>20.3811</td>
<td>-0.08692</td>
</tr>
<tr>
<td>14</td>
<td>1.360</td>
<td>162.545</td>
<td>21.9947</td>
<td>-0.08435</td>
</tr>
<tr>
<td>15</td>
<td>1.370</td>
<td>164.653</td>
<td>23.6307</td>
<td>-0.08692</td>
</tr>
<tr>
<td>16</td>
<td>1.380</td>
<td>165.443</td>
<td>25.2812</td>
<td>-0.08949</td>
</tr>
</tbody>
</table>
Following induction of anaesthesia, a reduction in both lung volume and compliance has been reported frequently in adults [1-4]. However, despite the fact that it is common practice for young infants to be paralysed and undergo ventilation during anaesthesia, rather than breathe spontaneously, few studies during the first few years of life have been performed to assess the effects of anaesthesia and neuromuscular block on ventilatory mechanics.

During the past few years, a new technique for measuring total respiratory compliance (Crs) has been developed and validated [5-9]. This technique, referred to commonly as the multiple occlusion technique, is based on the rationale that, if the infant's airway is occluded briefly during expiration, the Hering-Breuer reflex (HBR) may be induced, resulting in a brief ventilatory pause with relaxation of the muscles of ventilation. Providing that relaxation does occur during occlusion, the pressure which develops at the airway opening reflects the recoil pressure of the lung and chest wall [10]. Crs can be calculated by relating the volume occluded in excess of the end-expiratory volume to the corresponding value of relaxed pressure above atmospheric pressure recorded at the airway opening (fig. 1).

Adaptations of the occlusion technique have been applied both to anaesthetized adults and animals [1,11] and to spontaneously breathing infants [12-14] and infants undergoing ventilation [7, 15, 16]. The technique has been shown to be applicable to young children up to 4 years of age [17] and a strong cubic relationship between Crs and body length has been demonstrated during the first 1 yr of life in healthy infants [12]. As the occlusion technique avoids the use of oesophageal pressure measurements (which have been shown to be unreliable in preterm, sick, intubated or anaesthetized infants because of uneven distribution of pleural pressure [7,18, 19]), it should be of particular value when assessing ventilatory mechanics in anaesthetized infants. However, to our knowledge there are no published reports of such measurements.

SUMMARY
The multiple occlusion technique was used to study the effects of paralysis on ventilatory mechanics during anaesthesia. Total respiratory compliance (Crs) was measured during spontaneous breathing and following neuromuscular block with controlled ventilation in 23 infants. There was marked variation in response to paralysis: some infants demonstrated no change in Crs between the two states; others had values of Crs which were significantly higher during paralysis with controlled ventilation than during spontaneous breathing. A possible cause of these differences may be the type of controlled ventilation given during paralysis, with tidal volume directly influencing values of Crs obtained. The results of this study suggest that values of Crs obtained during spontaneous breathing and paralysis should not be used interchangeably until further studies have been performed to assess factors influencing Crs during controlled ventilation.
The aims of this preliminary study were to assess the use of the occlusion technique in anaesthetized children during the first 3 years of life, and to compare values of Crs obtained during spontaneous breathing with those measured during controlled ventilation, following administration of a neuromuscular blocking agent.

Approval for this study was given by the hospital Ethics Committee.

METHODS

The apparatus used to measure Crs is shown in figure 2. Pressure changes at the airway opening during airway occlusion in an anaesthetized infant breathing spontaneously.

Fig. 1. Tidal volume and pressure changes at the airway opening during airway occlusion in an anaesthetized infant breathing spontaneously.

Anaesthetic bag
Fresh gas flow

Pneumotachograph
pressure ports

Tracheal tube

Fig. 2. Patient system used for measurement of Crs. The flow signal measured with the pneumotachograph was integrated to give tidal volume.
(\(\Delta P_{\text{ao}}\)) were measured at the apparatus end of the tracheal tube using a Validyne MP45 transducer (\(\pm 5\) kPa). Flow was measured with a Fleisch pneumotachograph size 0 in infants younger than 6 months of age and size 1 in older infants. The pneumotachograph was attached to a low pressure range (\(\pm 0.2\) kPa) Validyne transducer and the output was electronically integrated to provide the volume signal (\(\Delta V\)). A bias flow of gas distal to the measuring apparatus (6 litre min\(^{-1}\)) was used to permit administration of anaesthetic gases. An anaesthetic bag connected to the distal end of the breathing system enabled manual ventilation to be introduced following administration of the neuromuscular blocker. The deadspace of the system was 7–15 ml, according to the pneumotachograph used, and resistance 0.48 kPa litre\(^{-1}\) s at a flow rate of 100 ml s\(^{-1}\).

A manually operated shutter placed proximal to the pneumotachograph was attached to the tracheal tube using a suitable low-deadspace connector. The pneumotachograph was thus not pressurized during occlusions. Recordings of volume, pressure and flow were made in real time onto u.v.-sensitive paper using an SE Labs 3000 UV recorder. Occlusions were timed using a Tektronix 5223 digitizing oscilloscope.

Normal hospital anaesthetic practice was adhered to as closely as possible. Infants weighing less than 10 kg were premedicated with pethidine compound 0.08 ml kg\(^{-1}\) (1 ml contains pethidine 25 mg, promethazine 6.25 mg and chlorpromazine 6.25 mg) given 1 h before operation. Those heavier than 10 kg were premedicated with papaveretum 0.4 mg kg\(^{-1}\) and hyoscine 0.008 mg kg\(^{-1}\). Anaesthesia was induced with cyclopropane in oxygen (\(F_{1\text{o}_2} = 0.5\)) until consciousness was lost, then maintained with nitrous oxide and 1–1.5% halothane in oxygen (\(F_{1\text{o}_2} = 0.5\)). Suxamethonium 1 mg kg\(^{-1}\) was given to facilitate tracheal intubation.

When tidal breathing had recommenced with a regular tidal volume and rate, measurement of \(C_{\text{rs}}\) was made during spontaneous breathing using an adaptation of the multiple occlusion technique [6, 12].

When the infant was breathing quietly through the apparatus, 15–25 expiratory occlusions were performed at different lung volumes within the tidal range. At least 10 breaths were allowed between each occlusion to enable stabilization of the end-expiratory volume (EEV). Providing that a pressure plateau of at least 0.2 s was achieved, indicating relaxation of the ventilatory muscles, the volume above EEV during each occlusion (\(\Delta V\)) was related to the corresponding pressure change at the airway opening (\(\Delta P_{\text{ao}}\)).

A non-depolarizing neuromuscular blocker was given to paralyse the child before surgery. During the subsequent controlled ventilation, which was performed manually, brief airway occlusions were performed at different lung volumes during passive deflation. Following release of the occlusion, the expired volume was related to the pressure plateau which had developed at the airway opening during the occlusion (fig. 3). At

---

**FIG. 3.** Tidal volume and pressure changes at the airway opening during airway occlusion in a paralysed, anaesthetized infant undergoing manual ventilation.
least 10 such occlusions were obtained with the infant undergoing manual ventilation for a minimum of five breaths between each occlusion.

No attempt was made to control the pattern of ventilation given by the anaesthetist during paralysis except to ensure that, following the release of each airway occlusion, adequate time was allowed during the subsequent passive expiration for the lung to reach its relaxed functional residual capacity before the next re-inflation. This was determined by observing the flow and pressure traces on the oscilloscope. All studies were completed within 20 min of the induction of anaesthesia.

**Analysis of results**

Care was taken to avoid potential errors in this technique by applying to data analysis strict criteria as established in this department [6], including rejection of data if there was evidence of active expiration or leaks during the occlusion. In order to avoid potential errors in the presence of dynamic lung elevation [20, 21], Crs was calculated as the slope of the volume-pressure data by least squares regression analysis. This took into account any intercept that might occur on extrapolation of the $V-P$ data, thereby preventing any underestimation of Crs [5]. A squared correlation coefficient ($R^2$) between 0.89 and 0.999 was found in infants in whom technically satisfactory data were obtained.

**Subjects**

Attempts to measure Crs during paralysis and spontaneous breathing were made following tracheal intubation in 74 anaesthetized infants and young children during the first 3 years of life. Although a satisfactory measurement of Crs was obtained during one or other of the states in 66 of the infants, reliable measurements during both spontaneous and controlled ventilation using Stocks' criteria [6] could be obtained in only 23 of these subjects.

Details of the 23 infants and young children (ages 1 month to 2 years 7 months) in whom a reliable comparison of Crs during spontaneous breathing and controlled ventilation could be made are included in table I. Of these children, 13 were known to have normal cardiopulmonary status, whereas the others had some form of neuromuscular, skeletal or renal disease which could potentially influence lung function.
Children undergoing thoracic surgery were excluded from the study.

RESULTS

The variability of absolute values of Crs obtained from individual infants (table I) largely reflected the fact that there is a rapid increase in Crs during the first 2 years of life [12, 17]. In order to standardize the effects of growth and enable meaningful comparisons to be made between infants, results were expressed as the ratio of Crs obtained during paralysis to that recorded during spontaneous breathing (Cp:Cs) in each infant. This ranged from 0.87 to 1.77 (table I). The 95% confidence interval for this ratio was calculated also for each infant. The width of such an interval reflects the scatter of volume data around the regression lines, the number of satisfactory occlusions obtained in each child and the pressure range over which they were collected [22, 23]: the wider the confidence interval, the larger the change that must occur between any two states before the difference is statistically significant.

In some infants, values of Crs during paralysis were similar to those obtained during spontaneous breathing, the narrow 95% confidence intervals of the Cp:Cs ratios encompassing unity (e.g. infants Nos 2, 36 and 31). In such infants, the small difference between states was not significant.
and was probably too small to be of clinical or physiological importance. Figure 4 illustrates the results from infant No. 2, in whom values for Crs were virtually the same in both states.

The calculated values of Crs during spontaneous breathing and paralysis were similar in many of the infants with 95% confidence intervals for the Cp:Crs ratios including unity and high P values, indicating that these differences were not significant. However, in some of these infants (e.g. infants Nos 13, 60 and 59) wide confidence intervals occurred indicating that, although a marked difference between the two states may have been present, there was insufficient evidence to judge conclusively. Figure 5 illustrates the results from infant No. 60. By contrast, other infants (e.g. infants Nos 58, 73 and 65) demonstrated an increase in Crs, with the whole of the 95% confidence interval for the Cp:Crs ratio being greater than unity. Even in infants with wider confidence intervals (e.g. infants Nos 20 and 58), the differences were so large that these increases were significant. Results from infant No. 58 are shown in figure 6. There were no occasions on which a significant decrease in Crs was observed during paralysis.

DISCUSSION

This study has demonstrated that the multiple occlusion technique may be applied to anaesthetized infants and young children during both spontaneous breathing and following administration of a neuromuscular blocking drug.

Measurements of Crs in at least one state were obtained in 66 of the 74 infants studied, despite adherence to the strict criteria for quality control established previously [6] and the constraints of studying anaesthetized infants before operation. These criteria included absence of leak on inspection of the volume and pressure traces, and a minimum of five pressure plateaux during occlusions in which there was no evidence of active expiration and which encompassed a pressure range of at least 0.3 kPa.

The major reason for failing to obtain satisfactory results during spontaneous breathing was persistent failure to relax during airway occlusion. During controlled ventilation, failures resulted predominantly from inadvertent application of positive end expiratory pressure or a leak around the tracheal tube which could not be controlled temporarily by gentle cricoid pressure. Lack of time was another major reason for failing to obtain both sets of results as every effort was made not to interfere with the normal operating schedule. A large number of the early failures were a result of developmental problems with the shutter mechanism.

The significance of our findings depends largely on the assumption that the same variable—namely the compliance of the passive respiratory system—was being measured during both spontaneous breathing and controlled ventilation. Following neuromuscular block, passive conditions could be ensured. However, the accuracy of the measurement during spontaneous breathing rests largely on the assumption that the change in tracheal pressure during airway occlusion represents passive elastic recoil of the respiratory system.
It is known that, in adults, anaesthesia may induce expiratory muscle activity [24]. Kaul, Heath and Nunn [25] measured EMG activity in the external oblique muscle and found that expiratory muscle activity developed within 29 min of inducing anaesthesia in 20 of the 22 adults studied. This activity decreased but was not abolished during inhalation of increasing concentrations of halothane.

All our infants received 1-1.5% halothane during anaesthesia, but the presence of active expiration was evident on many occasions, from the increase in tracheal pressure during airway occlusions. In some infants, this pattern was so persistent that Crs could not be calculated during spontaneous breathing. However, in the infants reported in this study, satisfactory pressure plateaux lasting at least 0.2 s, and at times as long as 1 s, were obtained sufficiently frequently to enable accurate calculation of Crs.

Although the vagally mediated Hering-Breuer reflex is thought to be weak or absent during normal tidal breathing in adults, it has been shown to persist in children up to 4 years of age [17]. However, without direct measurements of gastric pressure or EMG [26], it is not possible to exclude active expiration as a contributory factor to the differences observed in some infants. Unfortunately, accurate recordings of EMG from surface electrodes are difficult to obtain and would have significantly prolonged the duration of this study.

Several studies have been performed to validate the occlusion technique, using the presence of a pressure plateau to reflect muscle relaxation. Thomson (9) found no significant difference between Crs by the occlusion technique during spontaneous ventilation and total compliance from volume-pressure data following induction of apnoea in 12 infants. The same authors compared measurements of Crs by the occlusion technique with dynamic lung compliance in low birth weight infants and found that in infants in whom it was possible to obtain a satisfactory oesophageal pressure recording, Crs by the occlusion technique was always within 25% of dynamic lung compliance (Cdyn,L) [7]. As Crs includes the compliance of the chest wall, one would not expect values of Cdyn,L to agree perfectly with Crs. However, in a study on newborn lambs [8], static compliance of the chest wall was measured directly so that it could be subtracted from Crs to obtain a meaningful comparison with Cdyn,L. The mean static lung compliance of 2.38 (SD 0.54) ml cm H2O⁻¹ by the occlusion technique was not significantly different from dynamic lung compliance (measured from oesophageal pressure recordings) which was 2.58 (0.59) ml cm H2O⁻¹ in these healthy lambs breathing room air.

Various methods of differing complexity have been applied to assess compliance in anaesthetized infants [27-30], but not all have taken into account the compressible volume of the ventilator system or detailed how potential errors (such as leaks around the tracheal tube) have been recognized. The considerable variation in published results has been ascribed to differences in methodology, influence of volume history or the pressures utilized. The influence of volume history is unlikely to have been a major determinant of the variable response to paralysis seen in this study, as all infants received three inflations to 2.5 kPa before measuring Crs during the controlled ventilation.

In the presence of a long time constant and short expiratory time, there may be insufficient time for complete expiration to occur during spontaneous breathing, resulting in dynamic increase in lung volume [20,21]. As Crs was calculated by least squares regression analysis of the V-P data in this study, the presence of this phenomenon would have been evident from a negative intercept on the volume axis. However, all the infants reported in this study had marginal and insignificant intercepts (< 1 ml kg⁻¹) during spontaneous breathing, which would have been insufficient to contribute to any changes noted following paralysis.

Similarly, errors could occur during controlled ventilation if insufficient time were allowed for complete emptying of the lung following release of the occlusion [31]. However, we took care to avoid this problem by ensuring that zero flow and volume were achieved during passive expiration before the subsequent inflation. It appears likely, therefore, that the changes observed in some infants were not caused by technical errors but reflected a real change in the volume-pressure characteristics of the lungs during controlled ventilation.

Had we subjected the results of the 23 successful comparisons to a paired t test as is commonly the case in such studies, we should have demonstrated an increase in Crs during paralysis, that was significant at the 1% level.
RESPIRATORY COMPLIANCE IN ANAESTHETIZED INFANTS

However, this would have masked the very wide individual response that occurred. By determining the 95% confidence intervals for each child's results, the individual changes could be interpreted more readily. The most striking element of these results is the very wide variation in individual response to paralysis.

The confidence intervals for the individual Crs ratios were related directly to the scatter of the V/P points, the pressure range over which they were successfully collected, and the number of occlusions. The wider the confidence interval, the greater the difference between two measurements before statistical significance was reached. Therefore, in some infants (e.g. infants Nos 21 and 31) any real difference present could not be proven. However, in some infants there was conclusive evidence that there was no clinically or statistically significant difference between values of Crs obtained during spontaneous breathing and paralysis. In other infants there was a significant increase in Crs of at least 15% on paralysis, with the entire confidence interval for the Crs ratio exceeding unity.

In this laboratory, repeat measurements of Crs taken over time have been found to have values within 10% of each other (mean difference 5.1% in 13 infants). A change of 15% falls outside the variation between measurements and may also be of clinical importance.

To our knowledge, no similar comparative studies have been performed in infants and young children. Studies in adults have suggested that there is no significant difference between values of Crs obtained during spontaneous breathing and paralysis in anaesthetized subjects [3]. However, the power of some of these studies may have been too small to detect real differences because of the small number of subjects studied and the large scatter of results [1].

Results from two infants, who were excluded from the study because of the unusual marked scatter of their volume–pressure data (fig. 7) during paralysis (which prevented an accurate

![Figure 7](image_url)

**Fig. 7.** Volume–pressure plots during paralysis in infant A (age 1 month, weight 4.18 kg) and infant B (18 months, 11.3 kg).
assessments of Crs by regression analysis), provided an important clue as to the possible cause for the observed inter-individual variability of the results. On further examination of the time-based records from these infants, Crs was found to be changing progressively with time (fig. 8). Infant A showed a decrease with time and infant B an increase. The most likely explanation for these changes appears to be the pattern of manual ventilation administered during paralysis as evident from the continuous recording of tidal volume. In infant A, ventilation was very gentle following onset of paralysis, at a rate of 15 b.p.m., with peak pressures of 2–2.5 kPa. Initially, the measured Crs was similar to that during spontaneous breathing. Within 4 min it had halved. In contrast, infant B underwent ventilation at 60 b.p.m. with peak pressures of 2.5–3 kPa.

Lung volume is known to decrease during halothane anaesthesia, probably because of compression atelectasis [4, 32–34]. Breathing at this lower lung volume may occur along the stiffer portion of the S-shaped volume–pressure curve, reflected in lower values of Crs. Infant A may have undergone further atelectasis because of the low rate and volume of ventilation, achieving lung compliances progressively lower on the curve with time.

With larger tidal volumes, progressive re-inflation of atelectatic areas may occur, such that breathing occurs on the steeper portion of the curve with a resultant increase in Crs. Rate of ventilation may have contributed also to this effect, the more rapid rate used for infant B facilitating progressive increase in lung volume by preventing complete emptying between inflations before the occlusion.

The inter-individual variability in response to paralysis seen in this study may reflect the fact that some infants underwent more vigorous ventilation than others following neuromuscular block. Until this hypothesis is tested, values of Crs obtained during spontaneous breathing and paralysis should not be used interchangeably.
ACKNOWLEDGEMENT
This study was supported by the British Heart Foundation.

REFERENCES
Influence of tidal volume on respiratory compliance in anesthetized infants and young children

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DURING THE PAST few years a new technique for measuring total respiratory compliance (Crs) has been developed and validated (11, 20, 24, 32). This technique, commonly referred to as the multiple occlusion technique (MOT), has been applied to both spontaneously breathing (SB) and ventilated infants (11, 35). The occlusion technique avoids the use of esophageal pressure recordings, which have been shown to be unreliable in preterm, sick, intubated, or anesthetized infants because of uneven distribution of pleural pressure (12, 16, 35). Consequently this technique is increasingly being used for the clinical assessment of respiratory mechanics in ventilated infants (6, 35). However, to be able to interpret the results of such studies fully, a greater understanding of factors that may influence the measurements is required.

A previous study within this department suggested that, in anesthetized infants, there may be a relationship between Crs, measured by the MOT, and tidal volume administered during controlled ventilation (7). The potential influence of tidal volume on respiratory compli-

ance has been referred to by several authors (5, 9, 10, 23, 34), but any effects this may have on results obtained using the MOT do not appear to have been reported.

The aim of this study was to use MOT to determine the extent to which changes in tidal volume influenced Crs in anesthetized paralyzed infants and young children. Crs was measured during SB and during controlled ventilation with two different tidal volumes.

MATERIALS AND METHODS

Crs was measured in 20 infants and young children with no overt cardiopulmonary disease who were undergoing general anesthesia with neuromuscular relaxation (paralysis) for surgical or investigative procedures (Table 1). Children undergoing thoracic surgery were excluded from the study.

The apparatus used to measure Crs is shown in Fig. 1. Pressure changes at the airway opening (ΔPao) were measured at the apparatus end of the tracheal tube using a Validyne MP45 transducer (±50 cm H2O). Flow was measured with a Fleisch pneumotachograph, size 0 in infants under 6 mo and size 1 in older infants. The pneumotachograph was attached to a low pressure range (±2 cm H2O) Validyne transducer, and the output was electronically integrated to provide the volume signal (ΔV). A manually operated shutter placed proximal to the pneumotachograph was attached to the tracheal tube using a suitable low dead space connector. The pneumotachograph was thus not pressurized during occlusions. A bias flow of gas distal to the measuring apparatus (6 l/min) permitted the administration of anesthetic gases. An anesthetic bag connected to the distal end of the breathing system enabled manual ventilation to be introduced after administration of the neuromuscular relaxant. The dead space of the system was 7–15 ml, depending on the pneumotachograph used, and resistance was 4.8 cm H2O L−1 s−1 at a flow rate of 100 ml/s.

Recordings of V, pressure, and flow were made in real time on ultraviolet-UV sensitive paper using a SE Labs 3000 UV recorder. Occlusions were timed using a Tektronix 5223 digitizing oscilloscope.

Normal hospital anesthetic practice was adhered to as closely as possible. Seven infants were premedicated with triclofos sodium (75–100 mg/kg according to age) given 2 h preoperatively and atropine (0.02–0.06 mg/kg according to weight) given 0.5 h preoperatively. Two infants received the atropine only, and the remaining 11 infants, if <10 kg, were premedicated with denoral compound.
The known risks to this age group of using cuffed tubes considered necessary for successful measurements of Crs could be readily identified, cuffed tubes were not because we were satisfied that leaks around endotracheal and checking the resultant pressure and V traces (32). Peak inspiratory $P_{ao}$ between 25 and 30 cmH₂O. Absence of leaks was ascertained by performing a test occlusion. We were satisfied that leaks around endotracheal tubes. During the brief ensuing paralysis, manual ventilation was administered according to the anesthetists' preferred practice, all infants being well inflated with peak inspiratory $P_{ao}$ between 25 and 30 cmH₂O. Absence of leaks was ascertained by performing a test occlusion and checking the resultant pressure and V traces (32).

In two patients, where time allowed, LV ventilation was interrupted and cuffed tubes were not considered necessary for successful measurements of Crs. The known risks to this age group of using cuffed tubes made it ethically unjustified to introduce their use for research purposes when not required clinically. Once tidal breathing had recommenced with a regular tidal volume and rate, measurements of Crs was made during SB using an adaptation of the MOT (32, 36). With the infant breathing through the apparatus, tidal and Crs measurements were performed at different lung volumes within the tidal range. At least 10 breaths were allowed between each occlusion to enable stabilization of the end-expiratory level (EEL) (32). For occlusions where a pressure plateau of at least 0.2 s was achieved (0.1 s where respiratory rate >80 breaths/min), the volume above EEL during each occlusion ($\Delta V$) was related to the corresponding pressure change at the airway opening ($\Delta P_{ao}$). Crs was calculated by least squares regression analysis of the volume-pressure (V-P) data. The value thus obtained for Crs when the child was breathing spontaneously (CrsSB) served as a base-line measurement for each child to which measurements under paralysis could be referred. A nondepolarizing muscle relaxant, atracurium or d-tubocurarine, was then given to paralyze the child before surgery. With the onset of paralysis the anesthetist commenced manual ventilation mimicking the tidal volume and frequency displayed on the oscilloscope during SB.

Anesthesia was induced with cyclopropane $F\text{O}_2$ [inspiratory $O_2$ fraction ($F\text{I}_2O$) = 0.5] until consciousness was lost, then maintained with nitrous oxide, $F\text{O}_2$ = 0.5, and halothane (1-1.5%). Succinylcholine (1 mg/kg) was given to facilitate tracheal intubation with uncuffed tubes. During the brief ensuing paralysis, manual ventilation was administered according to the anesthetists’ preferred practice, all infants being well inflated with peak inspiratory $P_{ao}$ between 25 and 30 cmH₂O. Absence of leaks was ascertained by performing a test occlusion and checking the resultant pressure and V traces (32). Because we were satisfied that leaks around endotracheal tubes could be readily identified, cuffed tubes were not considered necessary for successful measurements of Crs. The known risks to this age group of using cuffed tubes made it ethically unjustified to introduce their use for research purposes when not required clinically.

Once tidal breathing had recommenced with a regular tidal volume and rate, measurement of Crs was made during SB using an adaptation of the MOT (32, 36). With the infant breathing through the apparatus, tidal and Crs measurements were performed at different lung volumes within the tidal range. At least 10 breaths were allowed between each occlusion to enable stabilization of the end-expiratory level (EEL) (32). For occlusions where a pressure plateau of at least 0.2 s was achieved (0.1 s where respiratory rate >80 breaths/min), the volume above EEL during each occlusion ($\Delta V$) was related to the corresponding pressure change at the airway opening ($\Delta P_{ao}$). Crs was calculated by least squares regression analysis of the volume-pressure (V-P) data. The value thus obtained for Crs when the child was breathing spontaneously (CrsSB) served as a base-line measurement for each child to which measurements under paralysis could be referred. A nondepolarizing muscle relaxant, atracurium or d-tubocurarine, was then given to paralyze the child before surgery. With the onset of paralysis the anesthetist commenced manual ventilation mimicking the tidal volume and frequency displayed on the oscilloscope during SB. Once paralysis was complete, Crs was measured at this low tidal volume (LV ventilation) by brief airway occlusions performed at different lung volumes during passive deflation. After release of the occlusion, adequate time was allowed during the subsequent passive expiration for the lung to reach its relaxed functional residual capacity (FRC) before the next reinflation. This was determined by observing the flow and pressure traces on the oscilloscope. The expired volume was related to the pressure plateau that had developed at the airway opening during the occlusion (Fig. 2). At least 10 such occlusions were obtained in each infant. Five breaths between occlusions were given to maintain adequate minute ventilation in the paralyzed state. Crs measurements during this initial period of manual ventilation represented Crs at a LV during paralysis (CrsLV). Because ventilation during SB and LV ventilation was depressed to a variable extent (Table 1), three to five inflations to a pressure of 25-30 cmH₂O were then given. This ensured all infants commenced high-volume ventilation from a standard volume history, which mimicked conditions at the beginning of the study. Manual ventilation was continued with tidal volumes approximately double those used during the low-volume study and Crs measurements repeated at this high tidal volume (CrsHV).

TABLE 1. Infant details

<table>
<thead>
<tr>
<th>Infant No.</th>
<th>Age</th>
<th>Weight</th>
<th>Height</th>
<th>Tidal Volume</th>
<th>Respiratory Res.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ml/kg</td>
<td>cm/s</td>
</tr>
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<td></td>
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<td>4.5</td>
</tr>
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<td>7.2</td>
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</tr>
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<td>71.0</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
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<td>63.0</td>
<td>4.5</td>
<td>10.8</td>
</tr>
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<td>11.3</td>
<td>90.0</td>
<td>5.8</td>
<td>5.7</td>
</tr>
<tr>
<td>20</td>
<td>0.1</td>
<td>5.0</td>
<td>56.5</td>
<td>4.2</td>
<td>4.4</td>
</tr>
</tbody>
</table>

* Not recorded at time of operation.
was resumed after CrsHV measurement and CrsLV remeasured. Care was taken to avoid potential errors in this technique by applying strict criteria to data analysis. These criteria included no evidence of leak on inspection of the volume and pressure traces and a minimum of five acceptable pressure plateaus during occlusions that encompassed a pressure range of at least 3.0 cmH$_2$O (32).

The pressure range quoted was the minimum accepted and set as such because of the relatively small pressures generated during SB and LV ventilation. Occlusions during the last third of expiration frequently result in failure to relax; thus an infant whose maximum pressure generated during occlusion at end inspiration is 5 cmH$_2$O may only have a pressure range of ~3 cmH$_2$O over which successful occlusions can be performed. In all but four V-P plots data were available for a pressure range of at least 4 cmH$_2$O.

Duplicate measurements of Crs for assessing reproducibility were possible in one infant during SB and in three infants during paralysis (while maintaining the same tidal volume and respiratory rate). All studies, including any reproducibility measurements, were completed within 20 min of inducing anesthesia. Hospital Ethical Committee approval was given for this study.

Statistical analysis. Crs measured using the occlusion technique is conventionally, as in this study, quoted as the slope of the V-P data calculated by least squares regression analysis to take into account any intercept that the infant be breathing above passively determined FRC (24, 36). A coefficient of determination ($R^2$) between 0.98 and 0.999 was found in 51 of 60 V-P plots analyzed. Of the remaining 9 V-P plots only 2 had $R^2$ values <0.95 (0.94 and 0.93, respectively).

The 95% confidence interval (95% CI) for each slope was also calculated. When comparing values of Crs from different states in individual infants, this CI demonstrated clearly the probability of any difference between the states being due to chance (1, 4, 8). Nonoverlapping confidence intervals indicate a statistically significant difference ($P < 0.05$) between the slopes.

For standards for the effects of growth and allow meaningful comparisons to be made between infants, values for Crs obtained during paralysis (CrsLV and CrsHV) were also expressed as a percent of the base-line value obtained during SB (CrsSB). Where there was evidence of linearity in the individual V-P data, in addition to linear regression analysis a polynomial was fitted ($V = aP + bP^2 + c$) as an indication of the significance of curvilinearity. All values of Crs in Table 2 are from linear regression analysis.

RESULTS

In the four infants in whom reproducibility was assessed, repeat measurements of Crs in the same state gave values between $-4.9\%$ and $4.7\%$ (mean $-1.3\%$) of those calculated on the first occasion. The results from a 4-mo-old 7.5-kg anesthetized child (infant 16) are shown in Fig. 3. During SB with a tidal volume of 25 ml and respiratory frequency of 73/min, CrsSB was 4.0 ml/cmH$_2$O (95% CI 3.8-4.2 ml/cmH$_2$O).

After paralysis, manual ventilation was commenced with a tidal volume of 30 ml and frequency of 57 breaths/min. CrsLV at 4.2 ml/cmH$_2$O (95% CI 4.1-4.4 ml/cmH$_2$O) was not significantly different from CrsSB. The small shift to the left of the LV V-P slope was merely the result of the minimal negative volume intercept (0.4 ml/kg) during SB.

When the tidal volume was increased to 70 ml (i.e., from 3.3 to 9.3 ml/kg), at a frequency of 43/min, Crs increased by 70% to CrsHV 7.0 ml/cmH$_2$O (95% CI 6.7-7.2 ml/cmH$_2$O). The wide separation between the confidence intervals for CrsLV and CrsHV indicates that the increase in compliance during HV ventilation was highly significant.

Evidence of linearity was seen during HV ventilation in four infants (6, 8, 10, and 19) in whom a significant negative intercept on the volume axis was also demonstrated on linear regression analysis. Because sufficient time for complete expiration was allowed after release of the occlusion during the paralyzed studies, extrapolation of the V-P data should pass through the origin (i.e., with no intercept). This was the case in all infants during the LV study. Curvilinearity of the data would explain the intercepts in these four infants during HV ventilation. Fitting simple polynomials to these data indicated that they were curvilinear ($P < 0.001$) despite an $R^2$ of 0.985 on least squares linear regression (Fig. 4). In the infants with evidence of linearity, a significant increase in Crs during HV ventilation occurred whether results were obtained from the mean ratio of volume to pressure or by linear regression analysis.

This pattern of increasing Crs with increasing tidal volume was demonstrated by all the infants as shown in Table 2. During LV ventilation there was a mean increase in Crs of 6.6% when compared with values obtained during SB. Seven infants demonstrated a fall in Crs of between 0.4 and 26%, whereas the remaining 13 showed a rise of between 3.9 and 45%. However, in all but three of the infants (5, 11, and 20), these changes were not significant at the 5% level as shown by the overlap of the 95% CIs (Table 2).

By contrast, when tidal volume was increased, CrsHV was significantly higher than CrsSB in every subject.
RESPIRATORY COMPLIANCE IN ANESTHETIZED INFANTS

1. FIG. 4. Alinear volume-pressure data from infant 6 during high-volume ventilation. A: line fitted by least-squares regression analysis \[ V = 16.3P - 25; R^2 = 0.985 \]. B: line fitted by polynomial analysis \[ V = 9.2P - 0.55 + 0.488P'; R^2 = 0.986 \].

2. TABLE 2. Individual compliance values

<table>
<thead>
<tr>
<th>Infant No.</th>
<th>Spontaneous Breathing</th>
<th>Paralysed Low Volume</th>
<th>Paralysed High Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.9 (5.7-6.1)</td>
<td>6.4 (5.5-6.8)</td>
<td>7.5 (6.9-8.1)</td>
</tr>
<tr>
<td>2</td>
<td>4.5 (4.0-5.0)</td>
<td>5.1 (4.5-5.3)</td>
<td>9.4 (7.8-11.1)</td>
</tr>
<tr>
<td>3</td>
<td>6.7 (5.5-7.8)</td>
<td>6.6 (6.2-7.0)</td>
<td>10.7 (8.2-13.2)</td>
</tr>
<tr>
<td>4</td>
<td>6.0 (5.7-6.4)</td>
<td>7.2 (6.5-8.1)</td>
<td>8.9 (7.3-10.3)</td>
</tr>
<tr>
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<td>1.8 (1.5-1.7)</td>
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</tr>
<tr>
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<td>16.3 (15.2-17.4)</td>
</tr>
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<td>6.8 (6.3-7.2)</td>
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<tr>
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<td>2.2 (2.1-2.3)</td>
<td>4.1 (3.9-4.4)</td>
</tr>
</tbody>
</table>

Values are expressed in ml/cmH\textsubscript{2}O with 95% confidence intervals in parentheses.

3. With no overlap between individual's 95% confidence intervals. The increase in Crs during HV ventilation, with respect to CrsSB, varied between 14 and 158% (mean 62%, \( P < 0.0001 \)).

4. When Student's paired t test was applied to the group results, a highly significant increase in Crs occurred. CrsHV ranged from 17.6 to 101% (mean 53%) greater than CrsLV ( \( P < 0.0001 \) ). Furthermore, considering the individual results, this increase was significant at the 5% level (or less) in all but one infant (4).

5. The interindividual variability of absolute results is predominantly a reflection of the rapid increase in tidal volume and Crs that occurs during the first 2 yr of life (18, 36). The changes in Crs are summarized in Fig. 5, which illustrates the large and significant change in Crs during HV ventilation and the small mean change but wide scatter during LV ventilation. To assess whether this variability in response was related to difficulties in exactly matching tidal volume during manual ventilation to that observed during SB, the relationship between percent change in tidal volume and percent change in Crs was examined. Although tidal volume was well matched during LV ventilation in some infants (1, 10, and 19; Table 1), in others there were considerable differences between the two states (infants 2, 4, and 9).

6. The mean change in tidal volume during LV ventilation was an increase of 11.6% (range —28 to 70%) over that observed during SB, whereas during HV ventilation tidal volume increased by 143% (range 31-320%). The relationship between Crs and tidal volume is illustrated in Fig. 6, which uses measurements obtained during SB as the base-line reference values ( \( R^2 = 0.58, P < 0.001 \) using least squares regression analysis). No significant relationship was found between respiratory rate and Crs ( \( R^2 = 0.01, P > 0.1 \) ).

In the two infants in whom CrsLV could be remeasured after the period of HV ventilation (infants 9 and 10), Crs fell from 9.4 and 9.3 ml/cmH\textsubscript{2}O, respectively, to 5.8 and
6.1 ml/cmH2O. This compared with initial values for CrsLV of 5.9 ml/cmH2O for infant 9 and 5.5 ml/cmH2O for infant 10.

DISCUSSION

The results of this study demonstrated that an increase in tidal volume was accompanied by a statistically and clinically significant increase in Crs in anesthetized infants and young children. This relationship occurred whether comparisons were made at different tidal volumes after paralysis or between SB and manual ventilation with an increased tidal volume. The similarity of Crs values obtained during SB and manual ventilation at similar tidal volumes suggests that neuromuscular relaxation itself has little effect on Crs.

The validity of the occlusion technique to measure Crs in SB infants depends on the ability to evoke the Hering-Breuer inflation reflex, with subsequent relaxation of the respiratory muscles, especially during occlusion (24). The occurrence of active expiration cannot be excluded completely without recording gastric pressure or abdominal electromyographic activity, equipment for which was not available when this study was performed. Evidence of respiratory muscle relaxation in this study was based on the presence of a pressure plateau during the occlusion.

In keeping with previous reports on anesthetized spontaneously breathing subjects (7, 30), the presence of active expiration was noted in many of our subjects as evident from increasing pressure at the airway opening during occlusions. This resulted in the failure of the technique in two infants in whom reliable data could not be obtained. However, among the 20 infants and young children reported in this study, active expiration was only an intermittent problem. By performing a large number of occlusions in each subject it was possible to obtain sufficient V-P data with satisfactory pressure plateaus to calculate Crs.

Ideally, ventilation during the low-volume study would have matched that observed during SB exactly, permitting a closer evaluation of the effect of paralysis per se on measured values of Crs. In practice, this proved to be very difficult, especially in the presence of respiratory rates of up to 90/min. Despite the difficulties, tidal volume during low-volume ventilation was maintained within 25% of that observed during SB in all but four of the infants studied.

In the presence of rapid respiratory rates and a long time constant, expiratory time may be insufficient for complete expiration to occur, resulting in dynamic elevation of lung volume (21, 36). Such conditions could occur in anesthetized infants because respiration tends to become rapid after induction of anesthesia and resistance may be significantly increased by intubation (15). In this study Crs was calculated by least squares regression analysis to take into account this phenomenon, which would be seen as a negative intercept on the volume axis on extrapolation of the V-P line (24). During SB only one infant (18) demonstrated a significant intercept of 2.2 ml/kg body weight. The remaining infants had marginal and insignificant intercepts (<1 ml/kg), which would have been insufficient to contribute to any changes noted after paralysis.

Before anesthesia, FRC is maintained substantially above residual volume and tidal breathing normally occurs along the linear portion of the curve (30). On induction of anesthesia in adults using the volatile gases, FRC has been shown to fall (13, 14, 25, 40), a change not seen during ketamine anesthesia in adults and children (17, 29, 38). This fall has been attributed to cephalad movement of the diaphragm and a decrease in respiratory muscle tone resulting in the development of atelectic areas in dependent parts of the lung (33, 37, 38). With a reduced FRC and small tidal volume, spontaneous breathing in the anesthetized infant may have taken place along the lower stiffer portion of the V-P curve (30). Because Crs measurements reflect only that portion of the V-P curve over which ventilation occurs, a reduced Crs would also be expected (2). A similar situation would probably occur after paralysis when ventilation is matched to the infant’s own efforts during SB.

During HV ventilation, the larger tidal volumes would have encouraged on the steeper portion of the V-P curve, explaining the alinearity of measurements observed in some infants. However, in the majority of infants the V-P data remained linear during the HV study (Fig. 3). The reason for this remains unclear. The administration of large tidal volumes after the standard volume history may have re-inflated atelectatic areas in some infants (37), resulting in an increased resting lung volume. With an increase in lung volume, ventilation could occur entirely along the steeper more linear portion of the V-P curve during the HV study.

The hypothesis that observed changes in Crs were primarily the result of measurements being performed over different portions of the V-P curve is supported by both the observations of Shulman et al. (30), who saw similar alinearity in anesthetized children, and by our finding that the effect of increasing tidal volume was shortlived. In both infants in whom measurements of CrsLV were repeated after the HV study, values immediately returned to their original low levels. This suggests that the observed changes were not merely the result of administration of the volume history before the HV study, particularly as a similar volume history had been given before the SB study.

In the original protocol it was decided not to repeat the volume history before LV measurements as we wished to assess the influence of paralysis on Crs while attempting to keep all other variables constant. Although administration of a volume history is unlikely to be the cause of the observed differences between the SB and HV measurements, further studies would be required to clarify its role in contributing to differences between values obtained for Crs during HV and LV ventilation.

The other factors that may contribute to changes in Crs during anesthesia and muscle relaxation paralysis have been discussed in detail in recent review articles (14, 25). Changes in parameters such as blood volume would appear to play a smaller role than the fall in lung volume.

The interpretation of our results would have been facilitated had simultaneous measurements of FRC been
possible. This was impractical without having prolonged anesthesia unduly in these infants. In addition, during HV ventilation high-pressure leaks frequently occurred during inspiration around the uncuffed tubes used in this age group. At the lower Pao of passive deflation such leaks were absent as confirmed by inspection of the pressure plateau during airway occlusions. In such circumstances Crs can be measured but FRC is unobtainable.

Results from previous studies to compare Crs during SB and after paralysis in anesthesia have been very variable (7, 27, 40). Studies in adults have suggested that there is no significant difference between values of Crs obtained during SB and paralysis in anesthetized subjects (40). However, the power of some of these studies may have been too small to detect real differences because of the small number of subjects studied and the large scatter of results (3). To our knowledge, no similar controlled comparative studies have been reported in infants and young children.

Studies using inflation techniques to measure Crs have frequently inflated the lungs to high pressures with resultant tidal volume equivalents of up to 50 ml/kg body weight (22, 27, 28). Appreciably lower values for Crs in anesthetized paralyzed infants were demonstrated by Reynolds and Esten (29) who inflated the lungs to predicted tidal volumes (for nonanesthetized infants) of ~10 ml/kg. However, direct comparisons are difficult because different techniques were used and different groups of infants studied.

Measurements of Crs in sick ventilated infants (31) have demonstrated a fall in Crs with an increase in continuous positive airway pressure. This is thought to have been the result of overdistension of areas of the lung possibly causing a shift to the stiff upper portion of the V-P curve. The current study measured relatively normal anesthetized infants, and the findings cannot therefore be extrapolated to the ventilated infant with respiratory disease. However, they do highlight clinically important differences that may arise in measurements made at what appears to be different parts of the V-P curve of the respiratory system.

It is therefore probable that sequential measurements of Crs made in ventilated infants may be profoundly influenced by changes in lung volume between measurements. The influence of tidal volume changes during mechanical ventilation on Crs measurements, and whether this differs from the effects during manual ventilation, has yet to be investigated. The importance of this variation in terms of ventilation and gas exchange also remains uncertain (14, 27, 40).

Conclusions. This study has demonstrated that MOT can be used in anesthetized infants and young children to compare measurements of Crs during SB and manual ventilation after administration of a neuromuscular relaxant. Our results demonstrate that significantly higher values for Crs can be obtained during manual ventilation with large tidal volumes than when anesthetized infants are breathing spontaneously. These results suggest that values of respiratory compliance during artificial ventilation may be considerably influenced by the pattern of ventilation at the time of measurement. Consequently, during artificial ventilation, the results of serial measurements of Crs within individuals or comparisons between subjects should be interpreted with caution unless a standard tidal volume is used.

We thank Simon Day for statistical advice during the study. This study was funded in part by the British Heart Foundation. This work was presented in part at the American Thoracic Society Meeting, Las Vegas, NV, May 1988. Address for reprint requests: M. E. Fletcher, Respiratory and Anesthetic Unit, Institute of Child Health, Guilford St., London WC1N 1EH, UK.

Received 22 February 1989; accepted in final form 1 November 1989.

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Respiratory Compliance in Anesthetized Infants


Respiratory compliance during sedation, anesthesia, and paralysis in infants and young children

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IN ADULTS, induction of anesthesia with volatile gases has been shown to cause a marked reduction in lung and total respiratory compliance (Crs) (6, 7, 14, 18). To our knowledge, no successful comparative studies have been performed to examine this effect in infants and young children. This has been due largely to the lack of a suitable technique that could be applied equally well to the anesthetized and nonanesthetized small child. The multiple occlusion technique for measuring Crs has now been used successfully to assess Crs in infants and young children during both spontaneous breathing and manual ventilation (6, 11, 16, 17). A previous study from this department demonstrated consistent changes in Crs between the anesthetized spontaneously breathing state and the anesthetized paralyzed state (3). During anesthesia with paralysis, Crs values were found to be dependent on the magnitude of tidal volumes used in manual ventilation. Increases in tidal volumes above those seen during spontaneous breathing resulted in significant increases in Crs. The aims of the present study were twofold. First, we wished to establish whether halothane anesthesia causes a reduction in compliance in spontaneously breathing infants and young children similar to that previously reported in adults. Second, if such changes did occur, we wished to demonstrate the extent to which they could be reversed by paralyzing the child and manually ventilating with tidal volumes greater than those observed during spontaneous breathing.

SUBJECTS AND METHODS
Sequential measurements of Crs by use of the multiple occlusion technique were made in infants and young children with no overt cardiopulmonary disease who were undergoing general anesthesia for surgical or investigative procedures. Children undergoing thoracic surgery were excluded from the study. Of 28 infants and young children entered into the study, two were excluded by emergency changes to operative list order that prevented data collection during anesthesia. In another eight children, measurements of Crs during spontaneous breathing after induction of anesthesia (CrsA) were invalidated by persistent failure to relax during airway occlusions. Two of these children also failed to relax during the sedated study. In one infant, a small leak not noted at the time of study invalidated results from the sedated study. Consequently, successful paired studies of Crs during sedation (CrsS) and CrsA were obtained in 17 infants and young children whose ages ranged from 1 to 28 mo.

In seven of these children, who were to be paralyzed for surgical procedures, two further measurements were made: 1) during halothane anesthesia with neuromuscular relaxation (paralysis) when ventilated with a low tidal volume that mimicked that observed during spontaneous breathing (CrsLV) and 2) during anesthesia-paralysis when tidal volume was increased to at least double that observed during spontaneous breathing, referred to as high-volume Crs (CrsHV). The results obtained during anesthesia for these seven children, which were published previously (3), are reproduced here to facilitate comparison with their CrsS values. The apparatus and technique have been described in detail in previous publications (3, 4).

During sedated sleep, tidal volume and airway pressure were measured via a face mask connected to a Fleisch no. 0 or 1 pneumotachograph and a manually...
operated shutter with pressure port, which was used to control brief airway occlusions.

During anesthesia the measuring apparatus was connected directly to the tracheal tube. A continuous flow of gas (6 l/min) from a T piece placed distal to the measuring apparatus permitted the administration of halothane, N\textsubscript{2}O, and O\textsubscript{2}. An anesthetic reservoir bag connected to the distal end of the breathing system enabled manual ventilation to be applied after administration of the neuromuscular relaxant. The reservoir bag was opened to eliminate positive end expiratory pressure (PEEP) during measurements. The dead space of the system was 7-15 ml, and resistance was 1.1-4.8 cmH\textsubscript{2}O • l\textsuperscript{-1} • s at a flow rate of 100 ml/s, depending on the pneumotachograph used. The pneumotachograph was calibrated with an appropriate gas mixture (N\textsubscript{2}O-O\textsubscript{2}) for the anesthetized studies and air for the sedated studies. All measurements were made with the child lying supine.

Normal hospital anesthetic practice was adhered to as closely as possible. Premedication was with triclofos sodium (75-100 mg/kg according to age) given orally 2 h preoperatively and atropine (0.15 mg-0.3 mg) given 0.5 h preoperatively. Once the child was sleeping quietly after triclofos administration, 15-20 brief intermittent airway occlusions were performed during expiration. Occlusions where a pressure plateau of at least 0.2 s was achieved (0.1 s if respiratory rate was >80 breaths/min during anesthetized studies) were accepted for analysis. Crs was calculated by least-squares regression analysis of volume-pressure data in which there was no evidence of a leak or active expiration and where the end-expiratory level was stable (16).

Anesthesia was induced with cyclopropane-O\textsubscript{2} (inspired O\textsubscript{2} fraction 0.5) until consciousness was lost and then maintained with N\textsubscript{2}O-O\textsubscript{2} (inspired O\textsubscript{2} fraction 0.5), and halothane (1-1.5%). Succinylcholine (1 mg/kg) was given to facilitate tracheal intubation with uncuffed tubes (3). During the brief ensuing paralysis, manual ventilation was administered with peak inspiratory airway pressures between 25 and 30 cmH\textsubscript{2}O.

Once tidal breathing had recommenced with a regular tidal volume and rate, measurement of Crs was made during spontaneous breathing as during sedated sleep to obtain CrsA.

Absence of leaks was ascertained by performing a test occlusion and checking the resultant pressure and volume traces (16).

A nondepolarizing muscle relaxant, atracurium besylate (0.5 mg/kg) or d-tubocurarine (0.4 mg/kg), was then given to paralyze the child before surgery. With the onset of paralysis, the anesthetist commenced manual low-volume ventilation mimicking the tidal volume and frequency displayed on the oscilloscope during spontaneous breathing.

Once paralysis was complete, Crs was measured at this low tidal volume (CrsLV) by performing at least 10 brief airway occlusions at different volumes during passive deflation, as described previously (41). After the release of each occlusion, adequate time was allowed during the subsequent passive expiration for the lung to reach its passive functional residual capacity (FRC) before the next reinflation. This was determined by observing the flow and pressure traces on the oscilloscope.

Because ventilation during spontaneous breathing and hence low-volume ventilation was depressed to a variable extent, three to five inflations to a pressure of 25-30 cmH\textsubscript{2}O were then given. This ensured that all children commenced high-volume ventilation from a standard volume history, which mimicked conditions at the beginning of the anesthetized study. Manual ventilation was continued with tidal volumes approximately double those used during the low-volume study, and Crs measurements were repeated at this high tidal volume (CrsHV).

An extended expiratory time was necessary during high-volume ventilation to prevent inadvertent administration of PEEP.

In two children (subjects 5 and 8), delays with preceding cases allowed repeat measurements of CrsLV to be made after completion of the CrsHV measurements. Manual ventilation was administered as during the first CrsLV study, and Crs was remeasured.

All studies were completed within 20 min of anesthesia induction.

Informed parental consent was obtained for each child, and hospital ethical committee approval was given for this study.

**Statistical Analysis**

Crs measured by the occlusion technique is conventionally, as in this study, quoted as the slope of the volume-pressure data calculated by least-squares regression analysis to take into account any intercept should the child be breathing above passively determined FRC (11, 17).

The coefficient of determination was between 0.93 and 0.99 in all but 2 of the 50 volume-pressure plots. The 95% confidence interval for each slope was also calculated. When values of Crs from different states were compared in individual children, this confidence interval demonstrated clearly the probability that any difference between the states was due to chance (1, 2, 5). Nonoverlapping confidence intervals indicate a statistically significant difference (P < 0.05) between the slopes. Group data were compared by Student’s paired t test.

To standardize for the effects of growth and allow meaningful comparisons to be made between children, values for Crs obtained during paralysis (CrsLV and CrsHV) were also expressed as a percentage of the baseline value obtained during sedation (CrsS).

**Results**

After induction of anesthesia, there was a reduction in Crs in all but one of the children (subject 16), as shown in Fig. 1, where Crs values during both states are plotted against body length. During anesthesia Crs was 0-58% (mean 34.7%) lower than in the same child during sedation (P < 0.0001). Furthermore, within individuals, these changes were significant at the 5% level in all but four of the children studied (subjects 2, 11, 16, and 17), as shown by the clear separation between the 95% confidence intervals for the two states in individual subjects (Table 1). After induction of anesthesia, tidal volume fell by
RESPIRATORY COMPLIANCE IN SEDATED AND ANESTHETIZED INFANTS

4.35 ± 1.33 (SD) ml/kg (P < 0.0001), whereas frequency rose by 2–41 (mean 19) breaths/min (P < 0.0001; Fig. 2). Group data showed an overall decrease in minute ventilation of 38 ± 69 (SD) ml • kg⁻¹ • min⁻¹ after induction of anesthesia, which was significant at the 5% level, although there was considerable intersubject variability (+55 to −184 ml • kg⁻¹ • min⁻¹).

There was no significant change in size of the volume intercept on extrapolation of the volume-pressure plots; intercepts averaged −1.49 ± 1.24 (SD) ml/kg during sedation and −1.64 ± 1.34 ml/kg during anesthesia (P = 0.7).

There was no relationship between the percent reduction in Crs on induction of anesthesia (median fall 41.9%, range 16.3–58%) was accompanied by a significant reduction in CrsS during sedation and CrsA during anesthesia (mean 9.8 ml/kg preanesthesia and 5.4 ml/kg postinduction) and increase in frequency in every case.

With paralysis and ventilation with a low tidal volume, values for CrsLV were similar to those for CrsA. The median reduction in CrsLV, with respect to CrsA, was 43.4% (range 1.9–55%), with no significant group change from CrsA to CrsLV. When tidal volume was increased, Crs increased significantly in every case, being within 10% of CrsS in all but one child, in whom there was a 31.4% increase with respect to CrsA.

As reported previously, Crs fell in both infants (subjects 5 and 6) in whom ventilation with low tidal volume was resumed after CrsHV measurement. The repeat CrsLV values were 5.8 and 6.1 ml/cmH₂O in subjects 5 and 6, respectively.

These changes in Crs were most closely related to changes in tidal volume, which accounted for ~50% of the variability in each state, rather than frequency or minute ventilation (Fig. 4B).

### TABLE 1. Total respiratory compliance during sedation and anesthesia

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Ag. mo</th>
<th>Length, cm</th>
<th>Sedated Crs, ml/cmH₂O</th>
<th>Anesthetized SB</th>
<th>Paralyzed LV</th>
<th>Paralyzed HV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.9</td>
<td>73.0</td>
<td>12.8 (11.1–14.5)</td>
<td>7.7 (6.1–8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8.3</td>
<td>74.0</td>
<td>11.1 (8.4–13.5)</td>
<td>7.3 (6.2–6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4.8</td>
<td>59.0</td>
<td>3.5 (2.0–4.1)</td>
<td>2.1 (2.0–2.3)</td>
<td>1.6 (1.5–1.7)</td>
<td>3.2 (2.8–3.6)</td>
</tr>
<tr>
<td>4</td>
<td>18.0</td>
<td>83.5</td>
<td>12.3 (11.8–12.9)</td>
<td>10.3 (9.7–11.5)</td>
<td>12.1 (10.7–13.5)</td>
<td>16.3 (15.2–17.4)</td>
</tr>
<tr>
<td>5</td>
<td>8.9</td>
<td>70.0</td>
<td>7.0 (5.8–10.5)</td>
<td>7.1 (6.5–8.9)</td>
<td>8.9 (5.5–6.6)</td>
<td>9.4 (5.2–10.1)</td>
</tr>
<tr>
<td>6</td>
<td>13.1</td>
<td>76.0</td>
<td>10.0 (6.0–11.3)</td>
<td>8.3 (7.4–10.7)</td>
<td>11.0 (9.0–13.5)</td>
<td>13.9 (11.4–14.4)</td>
</tr>
<tr>
<td>7</td>
<td>10.4</td>
<td>71.0</td>
<td>10.9 (10.1–11.8)</td>
<td>6.4 (4.9–5.9)</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>3.9</td>
<td>63.0</td>
<td>10.1 (8.4–10.7)</td>
<td>5.4 (4.8–6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>19.2</td>
<td>79.5</td>
<td>14.6 (14.0–15.2)</td>
<td>11.3 (10.7–12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5.1</td>
<td>83.0</td>
<td>12.8 (5.9–7.7)</td>
<td>3.2 (2.9–3.5)</td>
<td>3.7 (3.0–4.4)</td>
<td>6.4 (4.4–5.3)</td>
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<td>12.8</td>
<td>75.5</td>
<td>10.3 (6.7–12.3)</td>
<td>9.0 (7.5–10.1)</td>
<td>3.9 (13.1–14.4)</td>
<td></td>
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<tr>
<td>12</td>
<td>25.3</td>
<td>90.0</td>
<td>19.1 (17.5–20.5)</td>
<td>11.1 (8.8–15.3)</td>
<td>13.9 (11.4–14.4)</td>
<td>19.6 (17.5–21.7)</td>
</tr>
<tr>
<td>13</td>
<td>1.0</td>
<td>56.5</td>
<td>3.8 (2.3–4.3)</td>
<td>1.6 (1.2–1.9)</td>
<td>2.2 (2.1–2.3)</td>
<td>4.1 (1.9–4.4)</td>
</tr>
<tr>
<td>14</td>
<td>6.5</td>
<td>70.5</td>
<td>11.2 (9.9–13.5)</td>
<td>5.4 (4.8–6.0)</td>
<td></td>
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</tr>
<tr>
<td>15</td>
<td>6.9</td>
<td>67.0</td>
<td>7.9 (7.0–9.3)</td>
<td>5.8 (5.0–6.6)</td>
<td></td>
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</tr>
<tr>
<td>16</td>
<td>2.5</td>
<td>61.0</td>
<td>5.6 (4.8–6.3)</td>
<td>5.6 (4.8–6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>16.2</td>
<td>82.5</td>
<td>16.2 (14.8–17.5)</td>
<td>14.0 (11.2–16.7)</td>
<td></td>
<td></td>
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</tbody>
</table>

Values in parentheses are 95% confidence intervals. Crs, total respiratory compliance; SB, spontaneous breathing; LV, low-volume ventilation; HV, high-volume ventilation.
DISCUSSION

The results of this study demonstrate that a highly significant reduction in Crs occurs in spontaneously breathing infants and young children within 10 min of induction of halothane anesthesia. The magnitude of the change in Crs found in the 17 infants and young children reported in this study (34.7 ± 16.5% (SD)) is similar to that reported previously for adults (6, 10, 13, 18). As shown previously, during anesthesia Crs can be altered by manipulating the tidal volume administered during manual ventilation in the paralyzed child. Furthermore, it appears that the reduction in Crs seen during halothane anesthesia can be reversed in this age group by using tidal volumes approximating those seen during sedation.

Expiration effort during occlusions was unlikely to be responsible for the reduction in Crs after induction of anesthesia. Any recordings not demonstrating a relaxed pressure plateau during occlusion were excluded from analysis. Furthermore, values obtained during paralysis with low-volume ventilation, when there was clearly no possibility of phasic or tonic expiratory muscle activity, showed similar reductions of Crs with respect to the sedated state.

The changes in tidal volume and frequency that we observed while the children were breathing spontaneously during halothane anesthesia are similar to those in previous reports on children and adults (9, 12).

The reduction in lung compliance or Crs in adults has been attributed primarily to the reduction in intercostal muscle tone that occurs on induction of anesthesia with volatile agents (13). This in turn contributes to a fall in lung volume (FRC) (7, 18). Because Crs measurements made with the multiple occlusion technique reflect only the portion of the volume-pressure curve over which ventilation occurs, a reduction in outward recoil of the chest wall with consequent reduction in FRC combined with smaller tidal volumes could explain the marked reductions in Crs that have been observed during anesthesia. The volume dependence of Crs as demonstrated previously (3) is supported by our findings in the two children in whom repeat low-volume ventilation measurements were possible after CrsHV. Crs immediately returned to the low-volume values before the high-volume study.

It is possible that a change in the level of PEEP during manual ventilation could contribute to the observed changes in Crs. However, in this study considerable care was taken to avoid inadvertent administration of PEEP during the measurements.

The magnitude of these changes and their rapidity of onset and reversibility imply that absolute lung volume and ventilatory pattern may be the major factors influencing the change in Crs on induction of anesthesia.

Interpretation of results from the present study would have been facilitated by concurrent measurement of absolute lung volumes. Although FRC by helium dilution would be the method of choice for use in anesthetized infants, several technical problems need to be overcome...
before reliable measurements could be achieved. These include interference of helium analysis by halothane and the potential for fine leaks around uncuffed tubes.

Factors other than a fall in lung volume that may have contributed to the observed fall in Crs from sedation to anesthesia include increased lung surface tension and changes in thoracic blood volume after induction of anesthesia, residual effects of succinylcholine or atropine, and the influence of N₂O or the tracheal tube.

Dynamic elevation of lung volume due to laryngeal braking before anesthesia would be abolished by intubation resulting in a fall in FRC. Conversely, increased respiratory frequency combined with increased resistance from the tracheal tube could potentially result in increased dynamic elevation of lung volume after induction. However, only three children had a significant negative volume intercept on extrapolation of volume-pressure data from the sedated part of the study, and there was no significant change in the magnitude of this intercept after induction of anesthesia. It is therefore unlikely that the observed reduction in Crs can be attributed to any effect of the tracheal tube on lung volumes. The potential influence of upper airway compliance (15) is likely to have been minimal because the cheeks were supported during the sedated study, and the estimated compliance of the pharynx is extremely low compared with the values of Crs found during the sedated studies.

To our knowledge, no previous studies have compared values of Crs in infants and young children before and during halothane anesthesia in the same individuals. Indeed, there has been a tendency to view measurements made in anesthetized infants as the reference standard with which to validate measurements obtained in conscious infants (11, 17). In view of the marked reduction in Crs that occurs on induction of anesthesia in spontaneously breathing infants, the above practice is obviously inappropriate.

Clearly, results obtained using the now readily available and relatively simple techniques for measuring Crs and respiratory mechanics in this age group require careful interpretation. Although results from the anesthetized child cannot be directly extrapolated to the non-anesthetized state, it is obviously important that the mode of ventilation and tidal volume are recorded along with Crs values and, if possible, accompanied by measurement of lung volume.

Although we have shown that compliance values can be readily returned to preanesthetic values simply by increasing tidal volume in a paralyzed subject, there is evidence from studies in adults that the increase in volume is not accompanied by a proportional improvement in blood gases. Therefore, although Crs may be near normal, the other physiological changes accompanying halothane anesthesia are not so easily reversed, and disordered gas exchange remains a possibility that requires further investigation (7, 10).

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Received 18 July 1990; accepted in final form 10 November 1990.

REFERENCES

Respiratory Compliance in Infants—A Preliminary Evaluation of the Multiple Interrupter Technique

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Summary. Measurements of total respiratory system compliance (Crs) using the multiple occlusion technique (MOT) in spontaneously breathing infants can be difficult to interpret in the presence of an unstable end-expiratory level. Similarly, measurements using the passive flow volume technique (PFV) are invalidated if there is alinearity of the expiratory time constant (Trs), irrespective of respiratory effort. For possibly overcoming these problems, we assessed the feasibility of a technique using multiple interruptions of a single expiration (MIT), obtaining several pairs of volume-pressure data, from one expiration, which relate to a single end-expiratory level.

Crs was measured in 16 infants aged 0.5 to 20 months using the MOT, MIT, and PFV technique. The MOT and the MIT each failed in one (different) infant, both succeeding where the other failed. The PFV technique failed in five infants in whom no acceptable plateau of airway pressure during occlusion and no Trs could be obtained from a single breath. Failure to obtain a linear Trs was accompanied by failure of the MIT in only one infant. Individual differences between the MIT and the MOT were less than 9%. However, the PFV measurements varied from -16.3% to +25.7% of the values from MIT or MOT. The greatest differences between Crs values coincided with the greatest differences between volume intercepts of the extrapolated volume-pressure (MOT, MIT) and flow-volume (PFV) data.

From this preliminary study, the MIT proved as successful as the MOT, requiring fewer occluded breaths to measure Crs. In infants with a rapid respiratory rate, the data from several expirations can be merged and analyzed as for the MOT. Pediatr Pulmonol. 1992; 14:116-125. © 1992 Wiley-Liss, Inc.

Key words: Multiple occlusion; passive flow-volume and multiple interruption techniques compared.

INTRODUCTION

In 1976 Glinsky and co-workers first published data on the non-invasive measurement of compliance of the respiratory system (Crs) in spontaneously breathing infants using the airway occlusion technique. Since then numerous adaptions to their technique have been developed and applied. The measurement of total respiratory mechanics has now become a practical consideration in patients ranging from intubated preterm neonates to sleeping toddlers. Indeed, recent reports suggest that such measurements may also be possible in awake toddlers and young children.

Based on evoking respiratory muscle relaxation during a brief airway occlusion, two predominant techniques have been used to date: the passive flow-volume (PFV) or single breath technique, and the multiple occlusion technique (MOT). While simple to apply to a wide range of infants, the success of measurements with these two methods may be limited in some infants by specific recurring problems.

In the infant with an unstable end-expiratory level (EEL) (Fig. 1A), volume-pressure plots collected for the MOT tend to exhibit considerable scatter increasing the variance of the slope, and thus reducing the certainty of the final result (Fig. 1B). The time required to allow stabilization of EEL between occlusions increases the likely effect of changes in sleep state, or wakening, on the results.
The PFV technique depends on relaxation of respiratory muscles during the occlusion as well as during the subsequent “passive” expiration. In addition, a single expiratory respiratory time constant (Tns) is essential both to extrapolate volume to zero flow (for Crs = V/P) and to calculate the resistance of the respiratory system (Rrs). In infants failing to relax following release of the occlusion, and in those with alinearity of the expiratory flow-volume curve due to respiratory disease, the PFV technique cannot be applied, even if an adequate equilibration and relaxation plateau of airway pressure during occlusion is achieved.

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In an attempt to decrease the time required for data collection and analysis for MOT measurements of Crs, without dependence on a passive expiration with a linear flow-volume relationship, as in the PFV analysis, the possibility of performing multiple interruptions during a single expiration was re-examined.

Initially described by Gottfried et al, and used by his group to measure Crs in spontaneously breathing anesthetized cats and mechanically ventilated adults, the multiple interruption technique (MIT) has been applied more recently to measure Crs in spontaneously breathing anesthetized children. Multiple interruptions (brief occlusions) of a single passive expiration result in several pairs of V-P data that have a common EEL (Fig. 2A,B). In theory, collecting data in this manner should result in more V-P points acquired over a shorter time period than for the MOT, thus reducing the variability of the data.

The aims of this study were: 1) to assess whether the MIT could be applied successfully to sedated infants, with and without lung disease, during the first 2 years of life, and 2) to evaluate the potential advantages and limitations of the MIT in comparison with the MOT and PFV techniques.

MATERIALS AND METHODS

Subjects

Measurements of Crs by MOT, PFV, and MIT were attempted in 16 infants, aged 0.5 to 20 months. Nine of these were healthy infants recruited for an epidemiologi-
PFV measurements were attempted in all infants. End-inspiratory occlusions were held until airway pressure was seen to plateau. When there was evidence of early inspiration or a non-linear relationship between flow and volume following release of such occlusions, their duration was reduced until more prolonged and/or passive (i.e., linear) expirations occurred. Attempts were made to obtain five successful PFV measurements in every infant, allowing five to ten undisturbed breaths between occlusions. The detection of leaks around the face mask during data collection was facilitated by allowing the EEL to return to the pre-occlusion level, if necessary extending the time between interrupted breaths to allow this to occur.

Both analogue inputs (flow and airway opening pressure) were sampled at 50 or 100 Hz for the MIT depending on the infant’s respiratory rate. For MIT measurements sampling was initially set at 100 Hz during pilot studies but was subsequently increased for all infants to 200 Hz or occasionally 400 Hz, and the screen display scaled up to show each tidal breath in greater detail. Two infants, with a respiratory rate < 15/min. were measured at 100 Hz, and the remainder at 200 Hz. When sampling at 200 Hz, the definition of the displayed signals was similar to that seen on paper at a speed of chart approximately 75 mm/s. For PFV measurements analogue input sampling was set at 100 Hz.

Analysis

MIT data was analyzed as described previously. Crs being taken as the slope of the least squares regression line through the V-P data from all occlusions when airway pressure plateaus were > 0.15 s (with S.D. < 0.01 kPa for all samples over that period). A regression coefficient (R² squared correlation coefficient) of at least 0.9 was required before inclusion in comparisons.

MIT data were analyzed as individual V-P slopes for each breath, with at least three data points and R² ≥ 0.99. V-P data from an interruption were considered acceptable if the pressure plateau was at least 0.05 s with a S.D. of < 0.01 kPa in the samples over that period (10 samples at 200 Hz). The reported MIT value in each infant is the mean of the individual V-P slopes for all technically acceptable breaths (minimum two slopes). For both MOT and MIT, Crs was only calculated when V-P data encompassed a pressure range of at least 0.3 kPa. PFV data was accepted if: 1) the linear portion of the expiratory flow-volume plot encompassed at least 40% of the total expired volume; 2) R² > 0.99 for the slope obtained by least squares linear regression of the flow-volume data; and 3) the pressure plateau samples had a S.D. of < 0.01 kPa over at least 0.1 s. Differences between Crs values by the 3 techniques were assessed for significance using Student’s paired t-test. As a measure of agreement among the MIT and the MOT and PFV
TABLE 2—Individual Results for the Three Techniques*

<table>
<thead>
<tr>
<th>No.</th>
<th>MOT Crs (mL/kPa)</th>
<th>V int. (mL/kg)</th>
<th>MIT Crs (mL/kPa)</th>
<th>V int. (mL/kg)</th>
<th>PFV Crs (mL/kPa)</th>
<th>V int. (mL/kg)</th>
<th>Predicted Crs* (mL/kPa)</th>
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<tr>
<td>1</td>
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<td>—</td>
<td>88.5</td>
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</tbody>
</table>

*MOT, multiple occlusion technique; MIT, multiple interruption technique; PFV, passive flow-volume; V int., volume intercept.
*Crs predicted on body length in cm; Log Crs = (0.049L + 1.038).12
*Crs, 35.4 mL/kPa calculated from merged data points using MIT.

- The mean differences, the limits of agreement of the means, and 95% confidence intervals (CI) for the limits, were calculated, as described by Bland and Altman.12

RESULTS

The individual infants’ results from measurements of Crs using all three techniques are shown in Table 2.

Crs was measured successfully using the MIT in 14 of the 16 infants. Both infant nos. 6 and 16, in whom this technique failed, had lung disorders. In infant no. 6, who had CMV bronchiolitis, each interrupted breath resulted in only 1 to 3 V-P points over < 0.3 kPa and Crs could only be calculated from the combined V-P data from all breaths in which interruption had resulted in a satisfactory pressure plateau. This result was not included in any comparisons between techniques.

Infant no. 16, with severe cardiomyopathy, required < 0.3 s for airway pressure to plateau during occlusion; however, an inspiratory effort then prohibited further interruptions of expiration.

Two distinct patterns could be discerned in data from the MIT: 1) when the EEL was stable, the V-P data from different breaths were superimposed upon each other (Fig. 3); and 2) when the EEL varied between measurements, the V-P data from each breath resulted in a series of parallel slopes (Fig. 4). Interpretation of the data and identification of problems during the MOT, such as failure of airway pressure equilibration during occlusion, were comparable with the MIT. Figure 5 illustrates an interrupted breath from infant no. 10. During the initial interruption there was insufficient occlusion time for pressure equilibration, but data from subsequent interruptions were acceptable for analysis. Active expiration was evident in some breaths in certain infants, resulting in the exclusion of those data from analysis (Fig. 6). This did not occur in most infants, and at worst resulted in the loss of approximately four to five breaths out of up to ten attempts. Absence of passive conditions, due to possible abdominal and laryngeal muscle activity, was illustrated by infant no. 2 (Fig. 7). The breath illustrated in Figure 7A appeared well equilibrated during at least four interruptions. By the time the breath in Figure 7B was
recorded, 4 minutes later, the infant’s airflow pattern had been modulated, during both inspiration and expiration, continuing during the interrupted breath. The inappropriately low initial occlusion pressure may have been due to laryngeal muscle activity. Complete glottic closure would cause pressure measured at the airway opening to represent only supraglottic pressure. Laryngeal adduction, by increasing resistance to airflow, may prevent an equilibrated pressure being achieved within the duration of the interruption or occlusion. Gradual reduction in such laryngeal activity combined with some active expiratory effort would explain the increasing pressures and flows toward end-expiration (Fig. 7B).

As with the MIT, only one measurement failed when using the MOT, due to unacceptable scatter of the V-P data from 13 satisfactory occlusions ($R^2 < 0.9$). In this normal infant (no. 15), the MIT was successful, and in infant no. 16, in whom the MIT had failed, the MOT was successful.

Of the three techniques, the PFV was the least successful. In five infants it proved impossible to achieve, from the same breath, both a satisfactory pressure plateau during airway occlusion and a linear flow volume slope ($Trs$), following release of the occlusions from any one breath. Values for $Crs$ were obtained, however, for all
TABLE 3—Group Differences Among Crs Values Obtained by MOT, MIT, and PFV Techniques*

<table>
<thead>
<tr>
<th></th>
<th>Absolute difference [Mean (range), mL/kPa]</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>MIT to MOT (n = 13)</td>
<td>0.095 (−11.1 to 12.9)</td>
<td>0.96</td>
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<td>MIT to PFV (n = 10)</td>
<td>−4.76 (−31.1 to 8.9)</td>
<td>0.29</td>
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<tr>
<td>PFV to MOT (n = 11)</td>
<td>4.41 (−13.0 to 37.7)</td>
<td>0.35</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>% Difference [mean (range) %]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIT to MOT</td>
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</tr>
<tr>
<td>MIT to PFV</td>
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</tr>
<tr>
<td>PFV to MOT</td>
<td>2.87 (−9.1 to 25.7)</td>
<td>0.37</td>
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</tbody>
</table>

*For abbreviations, see Table 2.

For abbreviations, see Table 2.

The minimum time considered adequate for an acceptable pressure plateau during the MIT was set at 0.05 s for two reasons: First, after the initial equilibration, very rapid re-equilibration was the normal pattern of repeat interruptions (Fig. 2A). In infants measured during introduction of the technique, the second or subsequent interruptions were of longer duration. These extended interruptions, like the shorter ones, produced an almost instant pressure re-equilibration which was maintained until inspiratory activity commenced or the occlusion was released. Expiratory or inspiratory effort was as easily detected as during the MOT (Figs. 6, 7). Second, we accepted short occlusions (and pressure plateaus > 0.05 s) in order to achieve > 3 interruptions per expiration. The > 0.05 s plateau appeared to balance between the need for sufficient data per interruption, facilitating the observance of potential problems, and maximizing the number of interruptions per expiration. The short occlusions depended upon rapid signal sampling (200 Hz) and viewing of data on an expansive time scale. The brief pressure plateau during the MIT was only feasible due to the pre-existing airway pressure equilibrium and was therefore inappropriate for MOT or PFV.

Since V-P data from the MIT and MOT were closely comparable, and pressure equilibration is assumed to have occurred during successful MOT occlusions, it is reasonable to assume that equilibration had similarly occurred during the shorter MIT interruptions. This would suggest that the assumptions described above were valid.

Failure to achieve an adequate initial pressure plateau using the MIT did not necessarily result in the loss of the complete interrupted expiration (Fig. 5), as it would with the MOT or PFV technique.

In many infants, initial equilibration of airway pressure could take longer than 0.5 s. In infants nos. 4 and 5 reaching a linear Trs failed (it took > 0.5 s for an acceptable pressure plateau to occur; as the duration of occlusion was increased, the incidence of expiratory effort or early inspiration also increased). The PFV technique in such infants is therefore more dependent on a rapid initial pressure equilibration, than either the MIT or MOT.

Passive expiration following release of the occlusion was not a prerequisite for the MOT but the MIT required relaxation throughout the expiratory interruptions, and the PFV technique a totally passive expiration. While the PFV technique failed in infants nos. 4, 5, 11, and 15, mainly because of failure to achieve airway pressure plateaus, in these same four infants MIT was successful, even when an equilibrated pressure plateau and linear Trs could not be achieved in the same breath. It appeared that in such infants the respiratory system was in an equally

five infants using MIT or MOT. Consistent linearity of the expiratory Trs caused failure of the PFV technique in one normal infant and in one with lung disease (no. 4 and 16). In both infants Crs could be measured by either MOT or MIT.

When comparing Crs values obtained by all three techniques, the greatest differences were found between the PFV and the other two techniques. Values for MOT and MIT should be similar since one is an adaptation of the other, the advantages of the MIT lying in the reduced time required for data collection, and a reduction in the scatter of data points due to changes in EEL or sleep state between occlusions.

Crs measured by MIT differed from that using MOT by less than 9% in all 13 successful paired measurements. With so few infants, no trend in differences associated with age, weight, or magnitude of Crs could be identified.

Table 3 shows that, whether in absolute terms or as percentages, no overall statistically significant group differences existed between the values obtained by the different techniques. However, when the differences were examined in greater detail, a relatively poor agreement between the MIT and the PFV technique was found (Table 4). Although the group mean difference was less than 3% in all comparisons, individual differences varied from +26% to −16%. The greatest differences between Crs values tended to coincide with the greatest differences between the volume intercepts of the extrapolated V-P data (MOT or MIT) and extrapolated flow-volume data (PFV technique), as illustrated by infants nos. 3, 12, and 13 (Table 2).

Exchanging the data as suggested by Bland and Altman, 2 Crs obtained using the MIT may be up to 14.6 mL/kPa less than, or 14.4 mL/kPa greater than that measured for the same infant using the MOT (Table 4). The limits of agreement are less good between the MIT and the PFV technique (from −31.4 mL/kPa to +21.9 mL/kPa), and the 95% CI for these limits of agreement illustrate further the relatively poor agreement between the two. The wide 95% CIs for the limits of agreement reflect, in part, the small sample size of this comparison.

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relaxed state during airway occlusion for both MOT and MIT.

In infants with diseased lungs, particularly when respira-
tory resistance varies according to lung volume during
the tidal breath, linearity of Trs is likely to invalidate the
PFV technique. Thus, even during a fully relaxed expira-
tion, it may be impossible to obtain a linear Trs and hence
measure Crs accurately by the PFV technique.

**DISCUSSION**

The MIT has been applied successfully to measure Crs
in the tidal volume range in sedated infants aged from 0.5
to 20 months. By obtaining more than one occluded V-P
data point per expiration, the time required for data col-
lection and analysis was reduced, depending on the in-
fant's respiratory rate, to approximately 30% of that re-
quired for the MOT. Failure rate of obtaining a value for
Crs for the MIT and for MOT was the same but was
greater for the PFV techniques. The cessation of respi-
ratory activity during brief airway occlusion is thought to
be due to the Hering-Breuer inflation reflex. 
Both post-inspiratory diaphragmatic and laryngeal adductor
activity during expiration may increase the time between
onset of occlusion and equilibration of airway pressure,
even in the absence of disease. However, once relaxation
has been evoked and equilibration has occurred, re-equil-
ibration should be rapid following the release of a small
portion of inflation volume, as during the MIT.

Evoking a relaxed response to airway occlusion is least
successful at lower lung volumes. This frequently
leads to a paucity of data at lower occluded volumes
during the MOT. During the MIT, the respiratory sys-


<table>
<thead>
<tr>
<th>Techniques</th>
<th>Mean difference</th>
<th>Limits of agreement</th>
<th>95% CI</th>
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<td>-4.76</td>
<td>-31.4 to 21.9</td>
<td>-46.1 to -16.8 7.3 to 36.5</td>
</tr>
</tbody>
</table>

*For abbreviations, see Table 2.
data points to be collected. As several V-P points are collected per breath, the procedure would also be more rapid than with MOT. Thus, merging decreases the likelihood of changes in the infant’s respiratory pattern between repeat MIT measurements. Attempting to minimize artefacts due to alterations in EEL should not be confused with true variability of the infant’s Crs, which is unlikely to occur during such measurements. When measuring Crs by MIT in anesthetized or ventilated subjects, expiratory time has been commonly extended for the acquisition of V-P data. We have shown that this technique may be applied successfully to sedated, sleeping infants with respiratory rates of up to 63 breaths per minute. The MIT is particularly useful in the infant with a longer expiratory time as a greater number of V-P data points can be obtained. Potential problems encountered during MOT are as readily detected using MIT.

Although respiratory muscle activity might have influenced this data, the reproducibility of individual results and the close agreement with MOT suggest this did not occur. Muscle activity sensors such as EMGs would be required to clarify this.

The MIT offers a potential increase in the success of passive respiratory mechanics measurements in the non-anesthetized infant. Used in conjunction with a measurement of Trs it may provide a means of assessing Crs, Trs, and Rrs in infants in whom the PFV technique alone is unsuccessful.

ACKNOWLEDGMENTS

We thank Helena Childs for recruiting the normal infants included in this study, and A. Wade for statistical advice.

REFERENCES

Lung Involvement in Langerhans' Cell Histiocytosis: Prevalence, Clinical Features, and Outcome

S. Y. Ha, MRCP*; P. Helms, MRCP†; M. Fletcher, SRN‡; V. Broadbent, MRCP*; and J. Pritchard, FRCP*

ABSTRACT. In Langerhans' cell histiocytosis, the prognostic significance of pulmonary disease is controversial. The clinical and radiological features and lung function tests of Langerhans' cell histiocytosis patients presenting to a single tertiary referral center between 1981 and 1987 were reviewed. Age at diagnosis ranged from 2 weeks to 16 years (median 1.7 years) and the male-female ratio was 2:1. No child presented with lung involvement alone. In 18 (40%) of 45 patients with multisystem disease there was clinical and/or radiological evidence of lung pathology. Another 6 children (13%) with normal chest radiographs had abnormal lung function tests, suggesting subclinical ('occult') involvement. Those with overt lung disease tended to present at a younger than average age (median 0.6 years). The most common functional disturbance was reduced lung or respiratory compliance with reduced lung volumes. Patients with and without lung involvement showed a similar pattern of involvement of other organs, with skin and bone most commonly affected. Of the 45 children with multisystem disease, 38 (84%) survived 2 to 7 years after diagnosis; there was a similar proportion of deaths in children with and without lung involvement. It is concluded that lung involvement occurs in nearly half of young children with multisystem Langerhans' cell histiocytosis but does not adversely affect outcome. Pediatrics 1992;89:466-469; Langerhans' cell histiocytosis, lung disease.

ABBREVIATIONS. LCH, Langerhans' cell histiocytosis; RFT, respiratory function testing; CRS, respiratory system compliance.

Langerhans' cell histiocytosis (LCH), previously known as 'histiocytosis X,' is a disease with an unpredictable clinical course and prognosis. Its cause is unknown but a convincing body of recent evidence suggests that LCH is not a true malignancy.1 Involvement of more than one organ in the disease process ('multisystem disease'), in particular the hemopoietic system, liver, or lung, has been considered to worsen the prognosis.2 However, as far as lung involvement is concerned, our own clinical observations led us to question this claim.

Lung involvement is a well-known component of LCH. Isolated pulmonary histiocytosis has been repeatedly reported in adults, especially cigarette smokers, but rarely in children.3 In the past, documentation of lung involvement in LCH has largely depended on clinical assessment and chest radiographs;1,2 we could find no reports of systematic respiratory function testing in children.

To clarify these issues we aimed, in this study, (1) to calculate the prevalence of lung involvement in a consecutive series of LCH patients referred to a single institution, (2) to identify the pattern of abnormalities found on respiratory function testing (RFT), and (3) to examine the relationship between lung involvement and outcome.

PATIENTS AND METHODS

Between 1981 and 1987, LCH was diagnosed in 61 patients referred to our departments. For 56, tissue diagnosis was available. In the remaining 5 cases, the diagnosis was inferred from radiological and clinical features: all had one or more osteolytic lesions in skull or ribs with spontaneous healing. Details of management and outcome have been recently published elsewhere.4 This paper focuses on the natural history and prognostic significance of pulmonary disease.

The diagnosis of lung involvement was based on radiological findings including interstitial infiltrates, reticulonodular change, and a cystic or 'honeycomb' appearance. Clinical features suggesting lung involvement included tachypnea (respiratory rate > 60/min in infants and > 30/min in children), chronic or persistent cough, and/or chest wall retraction or tracheal tug. Lung biopsy was performed in only one case. In other patients the respiratory problem was clinically mild or moderate and an invasive confirmatory procedure was deemed inappropriate.

Whole-body plethysmography was used to measure thoracic gas volume in infants and very young children under the age of 2 years.6 We also measured dynamic lung compliance6 or respiratory system compliance7,8 together with airway resistance8 or total pulmonary resistance.9 At the time of testing, no child had clinical evidence of respiratory infection. It was not possible to perform reliable RFT in 2- to 5-year-olds, but cooperative children older than 5 years of age performed forced maximum expiratory maneuvers, helium dilution functional residual capacity tests, and CRS tests with the weighted spirometer technique.10 Respiratory function testing was deemed abnormal if results fell outside the 95% confidence interval of reference values measured in normal subjects, of a similar age, from our own laboratory and from summary data of previously reported values.7 Patients were defined as having 'occult' lung involvement if RFT results were abnormal but there were no respiratory symptoms or signs and chest radiographs were normal.

Systemic drug therapy (prednisolone and/or etoposide and/or vincristine) was used only when there was complicating failure to thrive or gross organ dysfunction.14 Time from diagnosis to most recent follow-up or to death for multisystem patients ranged from 2 months to 8 years (median 4.0 years). Differences in outcome between those patients with and without lung involvement were tested using χ² analysis and differences in age at presentation by rank sum tests.

RESULTS

Age at onset of illness ranged from 2 weeks to 16 years (median 1.7 years), but only 1 patient was older
Twenty-four (45%) of the children with multisystem disease had multisystem disease and none had lung involvement alone. In other parts of the body. In 2 cases these changes later, coinciding with exacerbations of disease activity. Group B ranged in age from 0.1 to 8 years (median 0.6 years) than the whole group (median age 1.7 years), although on ranking tests the difference was not statistically significant. The 6 patients in group B ranged in age from 0.1 to 8 years (median 0.5 years) at diagnosis.

In group A, 2 patients had only lung and skin involvement. In the remainder, (16 cases) two or more organ systems, other than lungs, were affected. Patients with and without overt lung involvement (ie, group A vs groups B and C) showed a similar pattern of involvement of other organs; skin and bones were most frequently affected (Fig 2). Five group A children had cough, 4 had rib recession, and 11 had tachypnea, but 7 patients (39%) had no respiratory symptoms or signs throughout their illness despite abnormal radiology. Chest radiography showed bilateral interstitial infiltrates in 13 patients, 2 of whom later developed radiological honeycombing. Infiltrates were invariably bilateral and of a reticular or reticulonodular pattern with or without peribronchial thickening. Four children had honeycombing at diagnosis and 1 had hilar lymphadenopathy. Two patients, aged 2 and 16 years, with honeycomb changes developed spontaneous pneumothorax. No patient developed a pleural effusion. Radiological changes were usually evident at presentation but in 2 patients occurred later, coinciding with exacerbations of disease activity in other parts of the body. In 2 cases these changes persisted for more than 1 year, but in the remainder have resolved.

Respiratory function testing
Respiratory function tests were performed on 13 patients from group A, either at presentation or when a radiological abnormality was first detected. All had abnormal RFT at some stage of the disease. It was not possible to perform RFT in 4 patients aged between 2 and 5 years (see "Patients and Methods") and one infant could not be adequately sedated.

Reduced compliance was the most frequent abnormality. Ten of 13 patients had a reduced CRS and 9 of 13 had reduced lung volume. A mixed restrictive and obstructive pattern was seen in 5 patients and a predominantly obstructive pattern in 1 of the patients with gross radiological honeycomb change. In 3 patients (aged 1, 3, and 6 months at presentation) RFT abnormalities were detected before the onset of radiological and clinical abnormalities. In a 1-month-old infant, RFT returned to normal as the disease activity remitted with treatment, although the radiological changes persisted for more than a year. In one 19-month-old, RFT 5 years after the onset of disease showed a restrictive pattern (reduced CRS and forced vital capacity).

All patients in group B showed a restrictive pattern with decreased CRS, with one also showing obstructive features with increased total pulmonary resistance. In two patients, hepatosplenomegaly might have contributed to the reduction in thoracic gas volume.

In group C, 11 of the 21 patients had RFT, with normal results in each case.

Outcome
Seven patients died. Each had multisystem disease with onset before 1 year of age. Four had lung involvement (3 overt, 1 occult). The remaining 38 patients with multisystem disease (84%) are alive 2 to 7 years after presentation, 25 of them free of evidence of active disease. Twenty-three (45%) of the UK-based patients, whose follow-up is complete, have no evidence of active disease 2 to 7 years after initial presentation.

![Diagrammatic representation of disease extent in all 61 Langerhans' cell histiocytosis (LCH) patients. The majority had multisystem disease and none had lung involvement alone. Twenty-four (45%) of the children with multisystem disease had either occult or overt lung involvement.](image)
Most of the 45 patients with multisystem LCH received some form of systemic therapy and although the proportion (17/18 = 94%) was greater in group A than in groups B and C (21/27 = 78%), the difference was not statistically significant. The presence of lung involvement did not appear to affect outcome (Fig 3).

**OUTCOME**

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<td>Group A</td>
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Fig 3. Pie charts showing the present status of patients with overt lung disease. Groups B and C with occult lung disease (group A), the most frequent abnormalities. In our patients with overt lung disease (group A), the most common abnormality was reduced compliance. Reduced lung volume was also seen and a mixed pattern of restrictive and obstructive changes was detected in a minority. It has been postulated that pulmonary infiltration and fibrosis leads to a reduced compliance and lung restriction, while the development of cysts and bullae results in air trapping and airflow obstruction. In our patients RFT abnormalities sometimes preceded the onset of radiological signs and clinical features and RFT returned to normal as the disease remitted. These features suggest that RFT are both sensitive and clinically useful in the detection and follow-up of lung involvement by LCH.

We were unable to assess alveolar-capillary block by the carbon monoxide test because of the young median age. We were able to perform RFT in only 10 of 21 patients considered not to have any lung involvement (group C) and may have underestimated the proportion of patients with asymptomatic lung involvement (group B).

It has been suggested, especially in children immunocompromised by corticosteroid or cytotoxic therapy, that lungs damaged by histiocyte infiltration are at increased risk of opportunistic infection including *Pneumocystis carinii*. Therefore, prophylactic cotrimoxazole is widely used in LCH patients with lung involvement who are receiving myelosuppressive and/or immunosuppressive agents.

We have confirmed previous reports indicating that lung involvement is relatively common in patients with multisystem LCH but does not worsen the prognosis. Respiratory function tests have a useful role in assessment and follow-up.

**ACKNOWLEDGMENTS**

Dr Hy was a Bill Marshall Clinical Fellow delegated by the Hong Kong Government to receive training at the Institute of Child Health (London, UK) and Dr Pritchard received financial support from the Imperial Cancer Research Fund (UK).

We thank Sheila Giles and Leigh Strangr for secretarial help.

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REVIEWS OF LAY LITERATURE IN CHILD CARE: WHAT PARENTS ARE READING


This text is designed to give the lay reader an overview to research on attentional deficits. Its brief chapters address a wide range of issues including difficulties in social, physical, academic, behavioral, and emotional development. Family dynamics and sibling problems are also discussed. Coverage, while clear and easy to read, is breezy, if not shallow. Much of this already short book is consumed by a question-answer and case study section which contributes little new information. Recommendations are sometimes controversial and include medicating without "drug holidays." The role of Candida albicans, reduced sugar intake, and vitamin therapy are viewed more enthusiastically than is warranted by current research. Most striking is the author’s lack of awareness of the huge concordance between attentional disorders and learning disabilities and his failure to consider the effects of adverse environments on children’s ability to attend and concentrate. The author also disregards a number of crucial treatment options including individual and family counseling, tutoring, special education, and parent support groups.

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